ARCHIVES OF PATHOLOGY

VOLUME 5 JUNE, 1928 NUMBER 6

PRIMARY (ESSENTIAL) HYPERTENSION

A STUDY OF FOUR HUNDRED AND TWENTY CASES *

E. T. BELL, M.D.

AND

B. J. CLAWSON, M.D.

MINNEAPOLIS

This report deals chiefly with the anatomic observations in 420 cases of primary hypertension that were studied by postmortem examination; the clinical observations are also included so far as they have a bearing on the problems that have attracted our attention.

Hypertension may be defined as an elevation of the blood pressure above the normal level. It may be subdivided into three types: (*a*) transitory or acute, (*b*) intermittent or fluctuating and (*c*) permanent or chronic.

Acute hypertension may result from emotional disturbances of various kinds (fear, anxiety, anger, worry and other emotions), from sensory disturbances such as severe pain (e. g., tabetic crisis, renal colic) or from unusual physical exertion. Persons who react excessively in this way to stimuli are believed to have some vasomotor instability; and it is possible that in an occasional case of this kind the hypertension may become permanent. In general, however, acute hypertension does not have such serious significance.

Injection of certain drugs (epinephrine and ephedrine) produces a sharp rise in the blood pressure, which lasts a short time.

Intermittent or fluctuating hypertension is apparently a well defined type. It is most frequently observed in women at the menopause. The systolic blood pressure may vary from 15 to 40 mm. of mercury from day to day, or even from hour to hour. Not many cases of intermittent hypertension have been well studied and followed. It is known that in those cases in which the condition occurs at the menopause, the patients usually recover; but a few authors believe that in some cases the hypertension becomes permanent. Our knowledge of this group is inadequate.

It is important to remember that the blood pressure must be found high on repeated examinations before the diagnosis of primary hypertension can be made on this observation alone.

---

* From the Department of Pathology, University of Minnesota.

Hypertension is a symptom rather than a disease and is due to many conditions. When it is associated with or caused by some known condition or disease it is called secondary; when the etiology is unknown, it is referred to as primary.

Secondary hypertension occurs in glomerulonephritis, toxemia of pregnancy, hyperthyroidism, urinary obstruction, certain suprarenal tumors, increased intracranial pressure, periarteritis nodosa, certain forms of nephrosis, arteriovenous aneurysm and aortic insufficiency. These secondary types will be discussed only so far as they throw light on the etiology of hypertension.

Primary or essential hypertension includes all chronic hypertension of unknown etiology. It is realized that this is probably not a homogeneous group, but the great majority of cases have a close similarity, clinically and pathologically. In the absence of any fundamental knowledge of etiology, it is convenient to name the disease by its outstanding feature, namely, high blood pressure.

This paper is largely an effort to define the disease more distinctly clinically and pathologically, and to show its relations to coronary sclerosis, apoplexy, arteriosclerosis and nephritis.

Primary hypertension is not a new disease. In statistics on deaths it usually appears under the clinical diagnosis of chronic myocarditis, chronic nephritis, arteriosclerosis or apoplexy; in pathologic reports, it appears as idiopathic hypertrophy and dilatation of the heart, coronary sclerosis or thrombosis, cerebral hemorrhage or encephalomalacia, chronic nephritis or primary contracted kidney.

Primary hypertension is not a sharply defined entity. Although typical instances are readily recognized, one frequently sees borderline cases which are doubtful. The cardinal features are high blood pressure, enlargement of the heart and renal arteriolosclerosis; but we must assign arbitrary limits to the first two, and we are confronted with a difficulty when one or two of the cardinal signs are absent.

CHARACTERISTICS OF HYPERTENSION

Blood Pressure.—In this study all cases in which there is a persistent systolic blood pressure of 150 mm. of mercury or higher, of unknown etiology, have been included as cases of primary hypertension regardless of other observations. In 220 of the 420 cases, the blood pressure was known to have been at this level. Hunter, who has made an extensive study of normal blood pressure in applicants for life insurance, gives the average in men 20 years old as 120 mm. of mercury systolic and 80 mm. of mercury diastolic. There is an average increase of 2 mm. in the systolic pressure and 1 mm. in the diastolic pressure every five years up to the age of 60 years, when the average systolic is 135 mm., and diastolic, 89 mm. Symonds finds that the increase with

age after 40 years practically disappears if pressures above 140 mm. of mercury (only 5.7 per cent of the entire group) are eliminated. Fisher finds a normal death rate in a group of 2,610 men from 40 years to 60 years old with an average systolic pressure of 142 mm. of mercury. Foster would apparently accept a blood pressure 15 mm. above Hunter's averages as within normal limits. Janeway considers 135 mm. of mercury before middle life and from 145 to 150 mm. of mercury thereafter as the upper limit of normal. It appears, therefore, that an arbitrary limit of 150 mm. of mercury is not too high in the group of men over 40 years old in which 90 per cent of the cases of hypertension occur, although it is apparent that some incipient and mild cases are excluded. It will be pointed out in the next paragraph that a diagnosis of hypertension is made when the systolic pressure is less than 150 mm. of mercury when there is a definite cardiac hypertrophy, since it is known that the pressure frequently falls when the heart begins to fail. The diastolic pressure has not been used as a basis for diagnosis.

Weight of the Heart.—In our experience, the average weight of the heart in persons over 40 years of age, with all cases of hypertension excluded, is about 280 Gm. for females and 330 Gm. for males (Bell and Hartzell). The upper limit of normal cannot be accurately determined. It is probable that the normal weight seldom exceeds 400 Gm. in the female or 450 Gm. in the male; but in order to be certain that only true hypertension is included we have adopted the arbitrary upper limits of normal as 450 Gm. for the female and 500 Gm. for the male. In cases in which the systolic blood pressure is unkonwn or is below 150 mm. of mercury, a diagnosis of primary hypertension is made when there is an idiopathic hypertrophy above these limits. A diagnosis of primary hypertension was made in 184 of our 420 cases on the basis of the weight of the heart, the blood pressure being unknown in 154 and below 150 mm. of mercury in thirty.

Of the 220 cases in which the blood pressure was known to be high, the weight of the heart in eighty was less than the assigned limits of 450 Gm. and 500 Gm. It is therefore obvious that we have excluded many cases of true hypertension in the group in which the blood pressure was not taken.

We have adopted the assumption commonly made by pathologists that primary hypertension was present in life when at postmortem examination we find a left ventricular hypertrophy of high degree that is not associated with valvular disease, adherent pericardium, syphilitic aortitis, chronic glomerulonephritis or hyperthyroidism.

A few patients have come to our attention who did not have elevation of blood pressure at any time during the period that they were under medical care, sometimes as long as six or eight months before death. It cannot be proved conclusively that they had hypertension, yet there

is strong evidence that they belong in this group. Patients with hypertension who have been under continuous observation for several years often show a normal blood pressure during the last few months of life. Cases of cardiac hypertrophy that have been studied for several years never belong to the doubtful group. Coronary disease and myocardial exhaustion often cause a fall of blood pressure, and when the patient is first seen in the late stages of the disease the blood pressure may not be high.

Renal Arteriolosclerosis.—This condition was present in approximately 90 per cent of our cases. It is one of the most constant features of the disease; but cases in which renal arteriolosclerosis was present have not been classed in the hypertensive group in the absence of a record of both high blood pressure and cardiac hypertrophy.

From the foregoing paragraphs, it is evident that a sharp distinction cannot be made between the hypertensive group and the normal, either clinically or pathologically. We cannot define hypertension clearly as we do typhoid fever or tuberculosis. Our diagnosis of primary hypertension is based on two points: (1) a persistent systolic blood pressure of 150 mm. of mercury or more of unknown origin; (2) a definite left ventricular hypertrophy (weight of heart, 450 Gm. or more in females, and 500 Gm. or more in males) not associated with any of the diseases known to cause hypertrophy.

Either of these conditions is sufficient to establish the diagnosis in the absence of the other.

A diagnosis of primary hypertension may be made clinically (1) when there is a persistent systolic blood pressure of 150 mm. of mercury or more not associated with any disease known to cause hypertension; (2) in a person suffering from chronic cardiac disease, with low or normal pressure, if there is a demonstrable cardiac hypertrophy of the left ventricular type not associated with any disease known to cause hypertrophy. The shape and size of the heart as seen in a roentgenogram made at a distance of 6 feet are often of great value in the diagnosis. A previous record of high blood pressure may be helpful.

CLINICAL COURSE

The great majority of patients consult a physician only after hypertension is well established, so that there has been little opportunity to study the earliest manifestations of the disease. Alvarez reports that before the patient develops any definite symptoms, it is usually possible to demonstrate a poor reaction of the heart to exercise and the appearance of cyanosis of the hands and legs on exposure to moderate cold. O'Hare and his co-workers find that 42 per cent of these patients give an early history of vasomotor weakness, such as nervousness, migraine, cold, sweaty, cyanotic hands, epistaxis and menorrhagia. We have

records of a few cases in which the blood pressure was only moderately elevated at first, but gradually rose to higher levels. Occasional cases are reported in which the hypertension was intermittent at first, but later passed into a permanent form.

We have little information as to the time of life when hypertension first develops. There are some reports on the blood pressure of college students. Alvarez found 22 per cent of young college men and 2 per cent of young college women with systolic pressure above 140 mm. of mercury. But this report was based on only one examination of each student, and evidently the factor of nervousness was not eliminated, since Diehl and Sutherland found that many students who had moderate hypertension at the first examination had normal pressure at a subsequent examination. The latter observers found only 4.4 per cent of men with intermittent or persistent pressure above 140 mm. of mercury and few with a pressure above 160 mm. of mercury. Follow-up studies were not made on these students, so that we do not know whether these moderate elevations of pressure in young men develop into the clinical cases that we see in adult life. In a few instances in our series, it is known that the patient had a normal blood pressure a few years before his symptoms developed. The records of routine health examinations will no doubt furnish important information on this important point in the future.

Some of the common early symptoms are headache, dyspnea, especially on exertion, vertigo, nervousness, irritability, insomnia, nocturia, poor memory, gastric distress, precordial pain, weakness, palpitation, blurring of vision, epistaxis, menorrhagia and cold, cyanotic extremities. Sometimes a little albumin is found in the urine. Hypertension is often discovered during a routine physical examination of a patient who is unaware of any illness.

The disease may persist for many years with or without important symptoms. Billings speaks of a woman who had a systolic pressure of from 200 to 260 mm. of mercury for forty years. The duration of symptoms is shown in table 1. It will be noted that in forty instances the disease was known to have been present over five years and in five over ten years. The table does not show the actual duration of the disease, but the time that the patient was aware of his illness.

In the vast majority of cases, symptoms and signs of serious involvement of the heart, brain or kidneys develop. The indications of cardiac disease are dyspnea, edema, cardiac pains of various kinds, cyanosis, palpitation, enlargement of the heart and murmurs. Death may occur suddenly from coronary occlusion.

The symptoms referable to the brain are headache, dizziness, nervousness, nocturia, fainting, irritability, loss of memory and transient or permanent paralyses.

The evidences of renal damage are unusually high blood pressure, severe retinal changes, progressive renal insufficiency (as indicated by laboratory tests), albuminuria and casts, and terminally clinical signs of uremia. Albuminuria alone is not evidence of serious renal disease, since it may be due to passive congestion or to temporary ischemia of the kidneys.

Commonly, a patient has symptoms referable to more than one of these three organs, namely: heart, brain and kidney; but, as a rule, late in the disease the symptoms referable to one organ predominate so that one may speak of cardiac, encephalic and renal types. The cardiac type may be subdivided further into a group in which there is progressive myocardial insufficiency or exhaustion and a group in which disease of the coronary arteries is the chief cause of the heart failure.

On the basis of the postmortem examination and the major clinical symptoms, we have subdivided our 420 cases into five groups, namely:

TABLE 1.—*Duration of Symptoms*

	Myocardial Insufficiency	Coronary Disease	Apoplexy	Renal	Total
0 to 3 months	20	23	22	6	71
3+ months to 6 months	15	5	4	3	27
6+ months to 1 year	20	4	7	2	34
1+ year to 3 years	55	9	14	9	87
3+ years to 5 years	31	6	7	7	51
5+ years to 10 years	19	8	3	5	35
10+ years to 16 years	1	0	3	1	5
Unknown	26	12	21	2	61
Totals	187	67	81	36	371

(1) a group with myocardial exhaustion or insufficiency, (2) a group with coronary disease, (3) encephalic group (apoplexy), (4) renal group (uremia) and (5) miscellaneous group (accidents and intercurrent diseases). There is some overlapping of the various groups, so that an occasional case must be classified arbitrarily. The distribution of the 420 cases in the five groups is as follows: myocardial insufficiency, 187; coronary disease, 67; encephalic group (apoplexy), 81; renal group, 36; miscellaneous group, 49.

DISTRIBUTION OF AGE AND SEX IN PRIMARY HYPERTENSION

Age Distribution.—The age at the time of death was known in 417 cases and was distributed in the decades as follows: from 10 to 20 years, 3 cases; from 21 to 30, 8; from 31 to 40, 28; from 41 to 50, 68; from 51 to 60, 137; from 61 to 70, 115; from 71 to 80, 48; from 81 to 90, 10 (fig. 1). The maximum incidence is between the ages of 50 and 70. The youngest patient was 13 years of age. Ninety and six-tenths per cent were over 40 years of age, and 74.3 per cent

were over 50 years. It is to be remembered that this is the age at the time of death. Presumably patients under clinical observation are younger. Hypertension as a cause of death is rare before the age of 30 years, only 11 cases being included in our series. The frequency of hypertension in our necropsy material is shown in table 2.

The relative frequency of hypertension can be seen more readily in figure 2, from which it appears that approximately 15 per cent of persons over 50 years of age have primary hypertension. This pro-

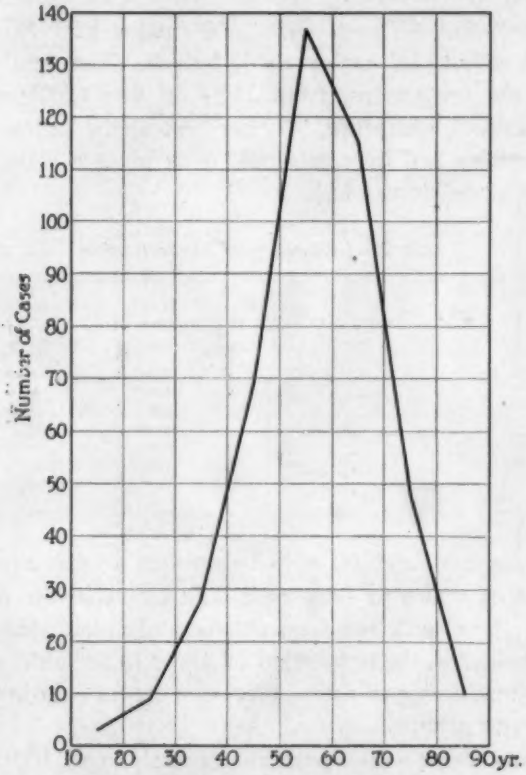


Fig. 1.—Age distribution in cases of hypertension.

portion may be too high for the general population, since there has been a lively interest in this disease in Minneapolis for several years, and greater effort is made to secure necropsies in these cases.

The age incidence in the several forms of hypertension is shown in figure 3. It will be seen that, with the exception of the renal, all the groups show the high incidence after the age of 40 years. This is true even of the miscellaneous group, which is largely composed of cases in which death was accidental. In the renal group, however, there are many younger persons, so that the average age in this group

is definitely lower than that in the others. Fahr also calls attention to the fact that in the renal case the patient is somewhat younger than in other forms of hypertension.

The miscellaneous group represents persons with hypertension, usually without clinical symptoms, corresponding to the initial stage already described. There are not enough cases to justify definite conclusions, but there is a suggestion that hypertension does not often begin early in life, since the age distribution is about the same as that in clinical cases of hypertension.

Sex Distribution.—There were 330 males and 90 females, a proportion of about 3.6 males to 1 female. The total number of necropsies in the age groups, from 21 to 80 was 4,578; males, 3,315, and females, 1,263. Therefore, 9.95 per cent of the males and 7.12 per cent of the females had hypertension. This gives a ratio of males to females of approximately 1.4 : 1.

TABLE 2.—*Frequency of Hypertension*

Decade	Total Number of Necropsies	Cases of Hypertension	
		Number	Percentage
21 to 30	685	8	1.2
31 to 40	867	28	3.1
41 to 50	920	68	7.4
51 to 60	976	137	14.0
61 to 70	768	115	14.9
71 to 80	290	48	16.5
81 to 90	51	10	19.6

With the same correction, it is found that in the coronary group the proportion of males to females is 2.7 : 1 and in the miscellaneous group 2.8 : 1. If only the renal, encephalic and myocardial insufficiency groups are considered, the proportion of males to females is only 1.1 : 1. A striking preponderance of males, therefore occurs only in the coronary and miscellaneous groups.

Thirteen and three-tenths per cent of males and 10.9 per cent of females over 40 years of age who were examined post mortem had primary hypertension. Approximately 15.8 per cent of males and 12 per cent of females over 50 years old had hypertension.

TYPES OF HYPERTENSION

GROUP I.—*Myocardial Insufficiency.*—In this group are included all cases that showed clinical evidence of chronic myocardial insufficiency for a period preceding death. In all except five, chronic passive congestion of the viscera was found at postmortem examination (table 5). In one of these five, death was due to pulmonary embolism. A satisfactory explanation of death was not found in the other four. Apparently

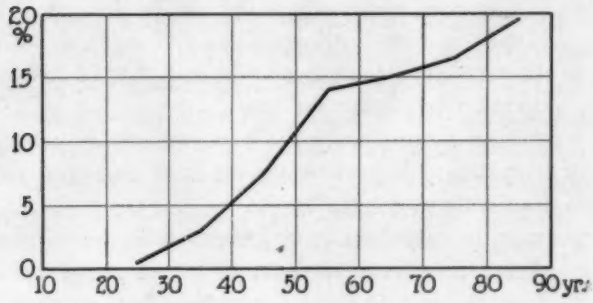


Fig. 2.—Percentage of deaths from hypertension.

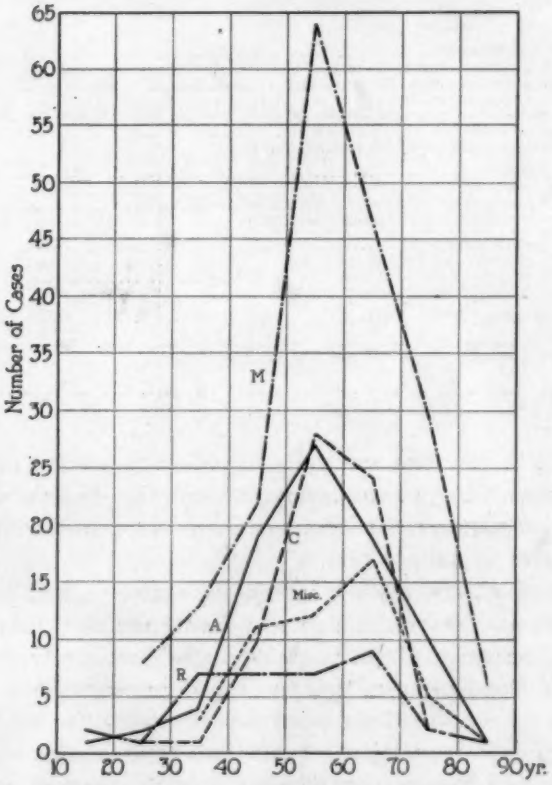


Fig. 3.—Age distribution of the several types of hypertension. *M* indicates myocardial insufficiency; *A*, apopletic; *C*, coronary; *R*, renal, and *Misc*, miscellaneous.

death may occur rather suddenly without venous stasis. Myocardial insufficiency is the commonest cause of death in cases of hypertension. It was the cause of death in 187 of 420 cases, or 49.3 per cent. If we include the coronary group, it may be said that in 254, or 60.4 per cent, death occurred from heart failure.

In order to show more clearly the observations on which we base the diagnosis of primary hypertension, we have arranged the cases in group I into four subgroups (table 3).

In subgroup A (ninety-four cases) the systolic blood pressure was known to have been 150 mm. of mercury or higher at some time. However, it was often below this level for a few days to several months before death. In ten cases of this group, the heart weighed less than

TABLE 3.—*Subdivisions of the Major Clinical Types*

	Cases
I. Myocardial insufficiency	187
A. Blood pressure above 150 mm. Hg	94
B. Blood pressure below 150 mm. Hg	26
C. Blood pressure unknown	53
(B and C, heart weight above 450 Gm., female; and 500 Gm., male)	
D. Blood pressure low or unknown	14
(Heart weight below 450 and 500 Gm.)	
II. Coronary sclerosis	67
A. Blood pressure above 150 mm. Hg	29
B. Blood pressure below 150 mm. Hg or unknown	38
(Heart weight above 450 and 500 Gm.)	
III. Encephalic group (apoplexy)	81
A. Blood pressure above 150 mm. Hg	64
B. Blood pressure below 150 mm. Hg or unknown	17
(Heart weight above 450 and 500 Gm.)	
IV. Renal insufficiency	36
V. Miscellaneous	49
(Heart weight above 450 and 500 Gm.)	
Total	420

450 Gm.; but in only two was the weight less than 400 Gm. (table 4). Of seventy-nine kidneys examined microscopically, 45.6 per cent showed severe arteriolosclerosis, 50.6 per cent, moderate, while the condition was not present in 3.8 per cent.

In subgroup B (twenty-six cases), the systolic blood pressure was never as high as 150 mm. of mercury during the time that the patient was under observation (from a few days to six months), and there was no record of blood pressure prior to the beginning of the illness. In all of these, the weight of the heart was over 500 Gm. and the hypertrophy was of the left ventricular type. It is assumed that a hypertrophy of this type and degree can develop only as a result of increased peripheral resistance, and that therefore hypertension must have been present earlier in the course of the disease. Some of the patients of group A would have been put into group B on the basis of their last admission to the hospital; but there was an earlier record of high blood

pressure. The cases of group B resemble those of group A in all essential features, clinically and pathologically, except that there is less renal arteriolosclerosis. Of twenty-two cases in which microscopic examination was made, severe renal arteriolosclerosis was found in 9 per cent and moderate in 77.3 per cent, while in 13.6 per cent, the condition was not present. The difference may be due to the small number of cases. The average size of the heart is greater than in group A, obviously because only large hearts were included (table 4).

Subgroup C includes fifty-three cases in which there was no record of the blood pressure. The diagnosis is based on the size of the heart. Clinically and pathologically, these cases correspond entirely with those in which the blood pressure was high. Of forty-eight cases

TABLE 4.—*Weight of Heart in the Various Forms of Hypertension*

Weight of Heart, Gm.	Myocardial Insufficiency				Coronary Disease		Apoplexy		Renal	Miscellaneous
	A	B	C	D	A	B	A	B		
250 to 299	0	0	0	0	0	0	5	1	1	0
300 to 349	1	0	0	0	1	0	5	0	2	0
350 to 399	1	0	0	0	2	0	8	0	2	1
400 to 449	8	0	0	6	3	0	8	0	5	2
450 to 499	13	0	4	8	5	0	13	1	3	1
500 to 549	7	8	11	0	5	19	13	5	5	25
550 to 599	15	8	15	0	7	9	5	3	10	13
600 to 649	12	1	8	0	3	5	2	2	2	6
650 to 699	18	3	4	0	0	2	3	1	3	0
700 to 749	11	3	5	0	1	1	0	0	0	0
750 to 799	10	2	5	0	2	2	1	3	2	1
800 to 849	3	1	0	0	0	0	0	0	0	0
850 to 935	3	0	1	0	0	0	0	1	1	0
Unknown	2	0	0	0	0	0	1	0	0	0
Total	94	26	53	14	29	38	64	17	36	49
Average	615	605	602	448	541	564	448	614	529	536

in which microscopic examination was performed, severe renal arteriolosclerosis was found in 45.8 per cent and moderate in 43.7 per cent, while the condition was not found in 10.4 per cent.

In the fourteen cases of subgroup D, the systolic blood pressure was unknown in ten and was below 150 mm. of mercury in four. None of the hearts weighed less than 400 Gm., and eight of them weighed over 450 Gm. These cases probably belong with groups B and C, but the weight of the heart is somewhat below the arbitrary limits of normal which we have used. Death was due to congestive heart failure just as in the other three groups. Of eight cases of this group in which microscopic examination was made, severe renal arteriolosclerosis was found in two cases and moderate in five, while the condition was not present in one case.

All the cases of chronic myocardial insufficiency of the idiopathic type that occur in our postmortem records have been included either

in group I or in group II. Apparently they are all associated with hypertension. There are no important distinctions between the four subdivisions of group I, but their arrangement in this way will show the nature of the available material.

Albuminuria was present from time to time and in varying degree in the great majority of the cases of group I. It does not indicate serious renal involvement. Subcutaneous edema, especially of the feet, or fluid in the serous cavities was usually found at postmortem examination.

GROUP II.—*Coronary Sclerosis.*—This group includes all cases in which the clinical history and results of the postmortem examination indicated that death was due primarily to coronary disease, and in which there was clinical evidence (high blood pressure) or pathologic evidence (size of heart) of primary hypertension (table 3). The clinical histories vary considerably, but may be grouped roughly into four types: (1) patient found dead, no clinical data available; (2) sudden death or death in an attack of angina pectoris, no previous

TABLE 5.—*Passive Congestion of the Liver*

	Myocardial Insufficiency	Coronary Disease	Apoplexy	Renal Insufficiency	Miscellaneous
None	5	23	42	8	31
Moderate	95	35	37	24	16
Severe	84	9	2	4	2

attacks or other symptoms; (3) sudden death or death in an attack of angina pectoris, history of one or more previous attacks but no evidence at any time previously of chronic myocardial insufficiency; (4) patient with chronic myocardial insufficiency who dies suddenly or in an attack of angina pectoris.

It will be noted that the fourth type might well have been classified with group I (myocardial insufficiency), the only difference being a terminal event, the manner of death.

Evidence of previous cardiac decompensation (passive congestion of the liver) was found in forty-four of the sixty-seven cases (table 5).

The pathologic evidence of death from coronary disease is: (1) thrombosis of one or more large branches with or without myomalacia or rupture; (2) chronic occlusion of some of the large branches with large myocardial scars; (3) chronic occlusion of some of the large branches with diffusely distributed scar tissue. Thirty-seven hearts of this group had been preserved and were studied by us in detail. Coronary thrombosis was present in twenty-seven, but not in the other ten. Evidently thrombosis is not the only cause of sudden death. It is well known to clinicians that coronary thrombosis does

not always cause death. Coronary thrombosis was found in five of seventy-five hearts of group I, in four of twenty-one hearts of group III, in four of fourteen of group IV and in one of six of group V. In these cases, it was not considered the chief cause of death. A high degree of narrowing of the coronaries is occasionally found in persons killed accidentally, so that in the absence of a thrombus, the pathologic diagnosis should be supported by clinical evidence.

The changes in the arteries resemble arteriosclerotic lesions found elsewhere. There is a thickening of the intima with degeneration, fatty infiltration and calcification. The damage to the heart results from narrowing and occlusion of the lumina of the arteries. Unlike the kidney, the arterioles rarely show sclerosis.

Relation of Coronary Disease to Hypertension: In our necropsy material, there were 136 deaths attributed to coronary sclerosis. Twenty-nine of these cases were classed as hypertensive because of the clinical record of high blood pressure and thirty-eight because of the size of the heart. Sixty-nine cases were not included in the hypertensive group

TABLE 6.—*Weight of Heart in Cases of Coronary Sclerosis in Which Hypertension is not Proved*

Below 300 Gm.	2 hearts
300 to 349 Gm.	7 hearts
350 to 399 Gm.	15 hearts
400 to 449 Gm.	29 hearts
450 to 499 Gm.	16 hearts

because the blood pressure was low or unknown and the size of the heart was below the extreme upper limits of normal. The weights of the hearts in the sixty-nine cases are shown in table 6.

The average weight of the sixty-four hearts from males is 411 Gm., and of the five from females, 337 Gm. Forty-five of these hearts are above the average normal weight, and there is, therefore, a suggestion that hypertension plays a rôle in this group also.

It is not surprising to find a normal or low blood pressure associated with advanced coronary disease, since the decreased blood supply prevents the myocardium from putting forth the extra effort required to maintain a high arterial pressure. A fall of blood pressure is not always a favorable sign in a case of hypertension, since it may mean advancing coronary disease. A number of our clinical records show a fall of systolic pressure from around 200 to about 140 several months before death, and in some of these, advanced coronary disease was found at postmortem.

Coronary sclerosis is more common and more intense in hypertensive than in nonhypertensive heart disease, as may be seen by reference to table 7.

In the preparation of this table, the coronary arteries were examined grossly by making a large number of transverse sections. They were then graded roughly into three groups: (*a*) those in which there was no demonstrable gross disease, (*b*) those with slight to moderate atheroma and thickening but without marked narrowing of the lumen and (*c*) those with marked thickening of the walls and narrowing of the lumen of at least one of the larger branches, or with thrombosis.

The nonhypertensive hearts comprise groups of syphilitic aortitis, old valvular defects and subacute bacterial endocarditis. Since the patients were usually younger than those in the hypertensive group,

TABLE 7.—*Coronary Sclerosis in Hypertensive and Nonhypertensive Heart Disease*

	Hypertension Percentage		Nonhypertension (All Ages) Percentage		Nonhypertension (Over 50 Years Old) Percentage	
	Right	Left	Right	Left	Right	Left
None	53.3	11.2	84.2	71.2	77.1	60.4
Slight or moderate	38.8	50.6	15.8	26	22.9	35.4
Severe	7.9	38.1	0	2.8	0	4.2
Thrombus	7.2	21	0	0	0	0
Number of cases	152		146		48	

TABLE 8.—*Coronary Disease by Decades, all Cases of Hypertension*

Age	Right			Left			Number of Hearts
	None	Moderate	Severe	None	Moderate	Severe	
11 to 20	1	0	0	0	1	0	1
21 to 30	1	1	0	0	1	1	2
31 to 40	7	2	0	2	6	1	9
41 to 50	10	4	1	0	11	4	15
51 to 60	32	24	4	10	28	22	60
61 to 70	19	18	6	2	21	20	43
71 to 80	7	10	1	3	6	9	18
81 to 90	2	1	0	0	1	2	3
Total							151

a separate column of those over 50 years of age was arranged for comparison. Age evidently has some relation to coronary disease, but hypertension is clearly a more important factor.

The relatively closer relationship of coronary disease to hypertension than to age is also brought out in table 8, which shows the incidence of coronary disease by decades in all the hypertensive hearts that were available for study.

The number of patients under 50 years of age is small, but it is significant that twenty-five of the twenty-seven showed some coronary disease, a much higher incidence than in the nonhypertensive hearts of all ages combined.

The frequency of renal arteriolosclerosis in the coronary group of cases of hypertension is about the same as that in the miscellaneous group, but definitely less than in the myocardial and encephalic groups (table 13). A comparison of renal arteriolosclerosis in the known hypertensive coronary group and in the other cases in which death resulted from coronary disease is given in table 9, from which it appears that it is present in 82.5 per cent of the former and 55.5 per cent of the latter. If one considers the entire 136 deaths which resulted from coronary disease, renal arteriolosclerosis was present in about 68 per cent. It is our experience that renal arteriolosclerosis seldom, if ever, occurs in cases in which hypertension can be definitely excluded, although it is sometimes seen associated with small hearts in cases in which the blood pressure is unknown. The presence of sclerosis of the renal arterioles is a strong argument for the presence of a primary hypertension at some previous time.

The argument that coronary disease itself causes the hypertrophy of the heart seems to us entirely unsound physiologically. It is con-

TABLE 9.—*Renal Arteriolosclerosis in Coronary Disease*

Degree of Arteriolosclerosis	Hypertensive Group, Percentage	Heart below 500 Gm. (Male) or 450 Gm. (Female); Blood Pressure Unknown or Below 150 mm. Hg, Percentage
None	17.5	44.4
Slight to Moderate	55.5	53.3
Severe	27	2 2

tended that the atrophy of some areas of the myocardium is followed by compensatory hypertrophy of the remainder, thus causing an increase in weight. It is difficult, however, to believe that a compensatory hypertrophy can occur in the presence of the obviously decreased blood supply that is usually found in these hearts. Furthermore, the actual weight of the scar tissue present is usually small, so that the hearts weigh much more than normal after all scar tissue is excised. One would need to suppose that the compensatory hypertrophy went far beyond the normal weight of muscle originally present.

It seems more reasonable to believe that when coronary disease develops in a case of hypertension it tends to prevent further cardiac enlargement and higher levels of blood pressure, and for this reason arteriolosclerosis is less pronounced.

On the whole, the evidence that coronary disease is closely related to primary hypertension is convincing; but we do not deny the existence of a nonhypertensive type. It is not known whether hypertension and coronary sclerosis are parallel phenomena or whether there is a causal relationship. This is the same problem that arises in connection with sclerosis of the renal vessels.

GROUP III.—*The Encephalic Group.*—This group includes cases of hemorrhage and encephalomalacia due to arteriosclerosis of the vessels of the brain. Cases of apoplexy due to embolism, hemorrhagic leptomeningitis, hemorrhagic pachymeningitis, hemorrhage from cysts or tumors or syphilitic arterial disease are not included. In a few of the cases of this group, the clinical course was that of chronic myocardial insufficiency, but the great majority were not clinical cases of heart disease. At postmortem examination, however, thirty-nine of eighty-one cases showed chronic passive congestion of the liver (table 5), indicating that myocardial insufficiency was present for some time before death. In the eighty-one cases of this group, there were fifty instances of hemorrhage and twenty-six of encephalomalacia. The brain was not examined in five cases, the diagnosis being based on the hemiplegia. In sixty-four cases the blood pressure was 150 mm. of mercury or higher, and the weight of the heart was above the arbitrary limits (450 Gm. female and 500 Gm. male) in thirty-two and below in thirty-two (table 4). The blood pressure was unknown in seventeen cases, but the hearts weighed above the 450 and 500 Gm. limits. It will be noted that there are many relatively small hearts in this group, which would not have been considered hypertensive had it not been known that the blood pressure was high.

The blood pressure readings were usually made after a stroke of apoplexy had occurred, and it may be that in some instances the hypertension was due to increased intracranial pressure and was not present before the stroke. Clinical experience has shown that an apoplectic stroke occasionally results in increased blood pressure. Cushing's experiments have established the fact that a uniform increase of intracranial pressure, above the level of the blood pressure, causes anemia of the medulla, which results in increased blood pressure. This condition is apparently fulfilled by a massive hemorrhage which spreads out all over the surface of the brain. A localized pressure on the brain does not commonly cause hypertension, since the pressure is not distributed to the medulla. Tumors of the brain seldom cause high blood pressure. The majority of intracranial hemorrhages are of the localized type and do not cause hypertension. In cases of encephalomalacia, which constitute about one third of the cases of apoplexy, there is no theoretical basis for increased intracranial pressure. It would seem, therefore, that increased intracranial pressure may have been responsible for the hypertension in some of our cases, but probably in only a few.

Besides the eighty-one cases which have been classified as hypertensive, there were sixty-four other cases of apoplexy in which the weight of the heart was below the upper limits of normal, and the

blood pressure was either unknown (fifty-seven cases) or below 150 mm. of mercury (seven cases). The weight of the heart was recorded in fifty-one of these and is shown in table 10.

The hearts, for the most part, were comparatively small, and the natural inference from this fact alone would be that they were not hypertensive. But it is to be remembered that there were a large number of relatively small hearts in the encephalic group of cases of hypertension (table 4), and that the blood pressure was not read in the great majority of this group. Hypertension cannot be ruled out on the available clinical data or the size of the heart.

TABLE 10.—*Weight of the Heart in Cases of Apoplexy*

Heart weight below 450 Gm. (female) or 500 Gm. (male). Blood pressure unknown or below 150 mm. of mercury.

Weight of Heart, Gm.	Number of Hearts
200 to 249	2
250 to 299	9
300 to 349	18
350 to 399	8
400 to 449	9
450 to 499	5

Average weight (51 hearts) 348 Gm.

TABLE 11.—*Renal Arteriolosclerosis in Cases of Apoplexy*

	Known Hypertension	Blood Pressure Unknown or Below 150; Heart Weight Below 450 Gm. (Female) and 500 Gm. (Male)
None	9.3%	17.9%
Slight to moderate	28.1%	57.1%
Severe	62.5%	25 %
Number of cases	64	52

A comparison of renal arteriolosclerosis in the cases of known hypertension with that in the other cases of apoplexy is shown in table 11.

Renal arteriolosclerosis was not so pronounced in the group in which hypertension was not proved as in the group in which it was known to be present; but it is significant that it was present in over 80 per cent. The blood pressure was above 150 mm. of mercury in sixty-four of seventy-one cases of apoplexy in which it was read. Of the 120 cases in which microscopic study was made (table 11), 86.3 per cent showed renal arteriolosclerosis.

One frequently sees references to cases of decrescent or senile apoplexy which are not considered related to hypertension because the heart is not hypertrophied. Our studies show that a small heart does not exclude hypertension. Nonhypertensive apoplexy seems to be relatively rare. The relationship between hypertension and the forms of

apoplexy under discussion seems to be close. It seems reasonable that hypertension hastens the progress of arterial disease in the brain and actually causes rupture of diseased vessels.

There is a common impression that sanguineous apoplexy (hemorrhage) is closely related to hypertension and that encephalomalacia (thrombosis) is related to senile or decrescent arteriosclerosis (Allbutt). In the cases of apoplexy in the known hypertensive group, there were fifty hemorrhages and twenty-six cases of encephalomalacia; and in the unproved group with smaller hearts, forty-two hemorrhages and twenty-one cases of encephalomalacia. We have no satisfactory evidence that encephalomalacia is less closely related to hypertension than hemorrhage.

Lippmann reports the systolic blood pressure in eighty-four cases of cerebral hemorrhage. The blood pressure was below 140 mm. of mercury in three, from 140 to 170 in fifteen, from 170 to 200 in thirty-seven and over 200 in twenty-seven. About two thirds of the cases showed definite to marked left ventricular hypertrophy (the weights were not given).

In fifty-two cases of encephalomalacia, the blood pressure was below 140 mm. of mercury in thirteen, from 140 to 170 in fifteen, from 170 to 200 in fourteen and over 200 in ten. Hypertrophy of the left ventricle was present in twenty-three. Lippmann's observations show that hemorrhage is more closely related to hypertension than encephalomalacia, but he has included six cases of embolism in younger persons which resulted from bacterial endocarditis and obviously did not have any relation to hypertension. In his entire group, he had 163 cases in which hemorrhage occurred and 66 cases of encephalomalacia.

GROUP IV.—*Renal Insufficiency.*—The diagnosis in this group is based on the structural changes in the kidneys. All the glomeruli in a section are counted and the number of hyaline or necrotic ones is expressed in percentage of the total number. When over 40 per cent are so damaged as to be nonfunctional, the case is placed in the renal group. This is, of course, not an accurate method, but it gives us some anatomic conception of the degree of damage. Apparently it underestimates the functional disturbance, since renal insufficiency is present in cases estimated anatomically at 40 per cent, and it is known that 60 per cent of the renal tissue may be removed without causing uremia.

In about two thirds of the cases of this group there was clinical or laboratory evidence (retention of metabolites, marked decrease of elimination of phenolsulphonphthalein) of renal insufficiency; in the others, the data were incomplete. In the chronic cases the kidneys were shrunken and granular, but in the acute cases there was little or no gross atrophy.

The involvement of the kidneys in the renal group differs only in degree from that of the other groups. In table 12 the degree of atrophy in the various groups is given, the estimation having been made by the method just described. The amount of renal tissue destroyed varies from 0 per cent to over 80 per cent.

The group with from 0 to 5 per cent of atrophy (56.2 per cent) is considered normal, since a few hyaline glomeruli are found in practically all kidneys. The surfaces of these kidneys are smooth.

The group with from 5 to 10 per cent of atrophy (22.8 per cent) shows a definite fine pitting of the external surfaces on close examination, but there is no thinning of the cortices. Only those with over 10 per cent of atrophy (21 per cent of 368 cases) show the characteristic finely granular surfaces, and only about 15 per cent of the entire group show a sufficient amount of atrophy to warrant the name of "contracted

TABLE 12.—*Renal Atrophy in Hypertension*

Percentage of Atrophy	Myocardial Insufficiency	Coronary Sclerosis	Encephalic Group	Renal Insufficiency	Miscellaneous	Total	
						Number	Percentage
0 to 5	90	46	32	..	39	207	56.2
5 to 10	45	13	19	..	7	84	22.8
10 to 20	12	2	6	..	2	22	6
20 to 30	6	1	4	..	..	11	3
30 to 40	4	1	3	..	..	8	2.2
40 to 50	..	..	..	4	..	4	1.1
50 to 60	..	..	..	5	..	5	1.3
60 to 70	..	..	..	8	..	8	2.2
70 to 80	..	..	..	14	..	14	3.8
80 to 90	..	..	..	5	..	5	1.3
						368	99.9

kidneys." Not all contracted kidneys cause uremia. Atrophy is due to disease of the arteries and arterioles, but a diseased vessel does not cause atrophy until its lumen is much reduced in size.

There are, therefore, all degrees of atrophy, from normal kidneys to small contracted kidneys. The term "primary contracted kidney" is applied somewhat arbitrarily to those that show a high degree of atrophy; but there is no sharp separation between these and kidneys with less atrophy. The same underlying vascular disease is present in all.

We have put only those with definite renal insufficiency in the renal group, 36 of 420 cases, or 8.6 per cent. The clinical phenomena that suggest serious renal involvement are (1) clinical signs of uremia (vomiting, nervous twitching, stupor, etc.); (2) decreased renal function as shown by laboratory tests; (3) unusually high blood pressure; (4) severe retinal lesions; (5) heavy albuminuria in the absence of cardiac decompensation, and (6) sudden, violent onset in a young person.

The clinical signs of uremia correspond to the retention of metabolites in the blood and appear only in the terminal stages. We have several records of normal blood urea nitrogen two weeks before death from uremia. The phenolsulphonphthalein test is more sensitive and shows decreased function much earlier; but when the heart is decompensated it gives too low a value, since it is influenced by passive congestion.

The blood pressure averages much higher with renal insufficiency than in the other groups. In thirty of thirty-six cases the average systolic pressure was 228 mm. of mercury; twenty-three were above 200, and three were above 300. The average systolic pressure in the encephalic group was 207, in the myocardial insufficiency group 188 and in the coronary group 180, but the blood pressure was above 200 mm. of mercury in about one third of the cases that did not show renal insufficiency, so that a high pressure alone does not establish the diagnosis.

Keith considers marked retinal lesions indicative of serious renal involvement. The acute fulminating type of hypertension usually ends in uremia.

Our thirty-six cases in the renal insufficiency group may be subdivided according to clinical data into three types.

Type 1: Acute Hypertension with Uremia: No clinical or pathologic evidence (cardiac hypertrophy) of long duration. Case 6, table 13, is the only one which fulfills these requirements. The details of this case are as follows:

Case 6.—A woman, aged 35, two weeks before her death first sought medical advice because of failing vision. Ophthalmoscopic examination revealed many recent retinal hemorrhages. The systolic blood pressure varied from 260 to 300 mm. of mercury. The phenolsulphonphthalein output decreased from 55 to 35 per cent (last test several days before death). She had a severe headache and became practically blind. The patient passed from a state of stupor into coma and died fourteen days after admission to the hospital. Postmortem examination revealed an absence of edema and fluid in the serous cavities. Moderate sclerosis of the aorta and severe sclerosis of the peripheral arteries was noted. The heart weighed 275 Gm. and the kidneys, 75 Gm. each. The surfaces showed many large, smooth depressions which corresponded microscopically to areas of acute atrophy resulting from fairly rapid closure of small arteries (fig. 4). Many of the small arteries showed hyalinization and necrosis of their walls, with almost complete occlusion of their lumina. The arterioles were largely necrotic and partially or completely occluded. Some of the glomeruli were infarcted (fig. 5). The larger arteries in the kidney showed relatively little change. There were no inflammatory changes in the arterioles or glomeruli.

Type 2: Chronic Hypertension Ending Acutely in Uremia: Hypertension known to be of long duration from the clinical history and weight of the heart. Eight of our thirty-six cases belonged to this group, namely, cases 7, 13, 14, 19, 22, 32, 34 and 36 (table 13).

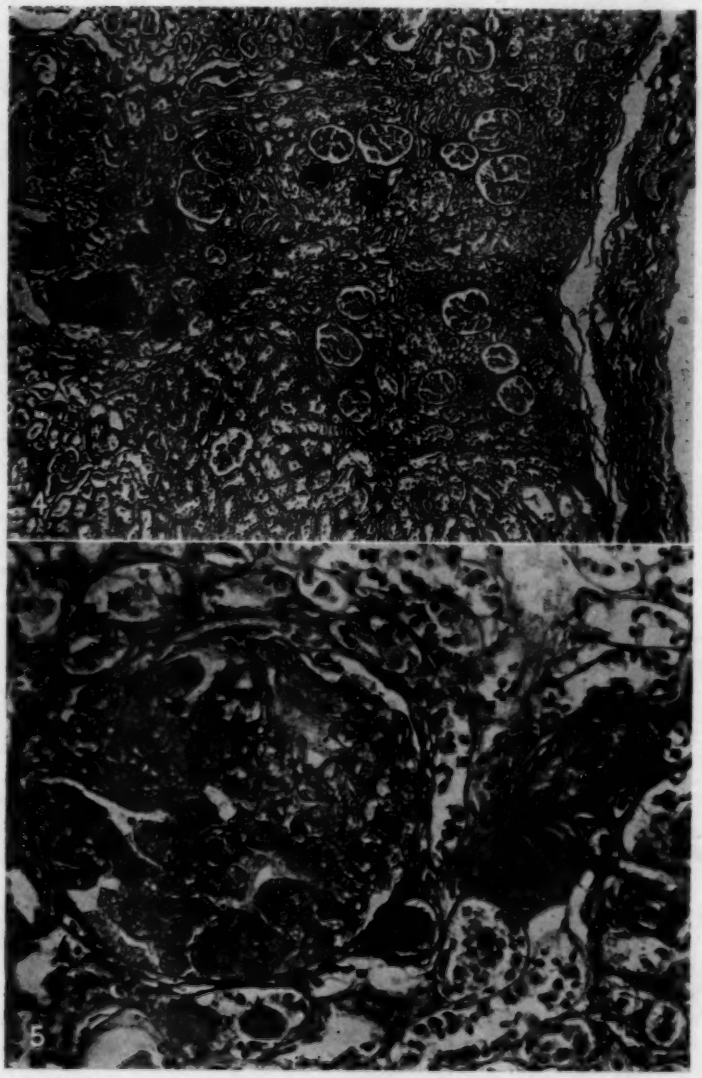


Fig. 4 (case 6, table 13).—Area of acute atrophy due to rather rapid closure of a small artery. The artery shows hyalinization and necrosis of its wall with almost complete closure of its lumen.

Fig. 5 (case 6, table 13).—Necrotic occluded arteriole with infarction of its glomerulus.

TABLE 13.—*Data on the Renal Group*

Number	Age, Years	Sex*	Known Duration	Blood Pressure	Degree of Atrophy	Weight of Heart, Gm.	Blood Urea Nitrogen	Closure of		Infarcted Glomeruli	Acute Glomerulitis	Hyaline Extension into Glomeruli	Type
								Small Arteries	Arterioles				
1	52	♂	3 years	230-130	80-90	680	—	+++	+	—	—	—	3
2	55	♂	8 months	?	50-60	500	—	++	++	—	—	—	3
3	50	♂	1 year	200-110	70-80	760	—	+++	+	—	—	—	3
4	70	♂	1 year	.....	70-80	650	—	+	+++	—	—	—	3
5	50	♀	5 weeks	.....	70-80	430	—	++	++	+	—	—	3
6	35	♀	2 weeks	200- ?	40-50	275	—	+	+++	+++	—	—	1
7	13	♀	8 years	260-190	60-70	325	107	+	+++	++++	+	+	2
8	38	♂	3 years	220-140	70-80	620	50	+++	+	—	—	—	3
9	82	♂	1 month	215-150	70-80	550	—	+++	+	+	—	—	3
10	51	♂	4 years	225-140	70-80	925	—	++	++	—	+	—	3
11	65	♀	4 years	240-105	80-90	435	156	+	+++	—	—	+++	3
12	67	♀	8 months	.....	40-50	500	—	+++	+	+	—	—	3
13	57	♂	4 months	220- ?	70-80	575	—	+++	+	—	—	+	2
14	34	♂	3 months	300-175	50-60	770	40	++	++	—	—	—	2
15	55	♀	3 years	220- ?	70-80	390	—	+	+++	—	—	+	3
16	68	♂	3 years	188- 95	50-60	580	54	+	+++	—	—	+++	3
17	65	♂	5 years	200-110	40-50	500	—	+++	+	—	—	—	3
18	73	♂	1 month	160-100	60-70	435	290	+++	+	—	—	—	3
19	43	♂	2 years	270-145	70-80	500	106	+	+++	++	++	—	2
20	35	♀	10 weeks	245-175	70-80	560	54	++	++	—	—	—	3
21	14	♀	5 years	240-160	40-50	300	—	++	++	—	—	++	3
22	38	♀	18 months	192-118	70-80	625	158	+	+++	+	—	—	2
23	49	♂	9 months	180-124	60-70	600	52	+++	+	—	—	—	3
24	33	♀	4 years	260-170	60-70	460	209	++	++	—	—	+	3
25	35	♀	1 year	265-170	50-60	420	192	++	++	—	—	—	3
26	57	♂	12 years	230-150	60-70	550	—	++	++	—	—	++	3
27	60	♂	10 years	.....	60-70	580	87	+++	+	—	—	—	3
28	27	♂	4 years	300-200	50-60	450	—	++	++	—	+	+	3
29	41	♂	10 years	228-138	70-80	580	150	+++	+	—	—	—	3
30	47	♂	3 months	245-120	60-70	450	45	++	++	—	—	+	3
31	70	♀	1+ years	.....	60-70	380	—	++	++	—	—	—	3
32	69	♂	2 months	185- 75	80-90	500	—	++	++	++	—	—	2
33	60	♂	1 year	194-114	70-80	550	150	+++	+	—	—	—	3
34	71	♂	2 years	160- 80	80-90	560	—	+	+++	++	—	—	2
35	66	♂	1 year	205-160	80-90	440	73	+++	+	—	—	—	3
36	46	♂	8 months	205-120	70-80	550	—	++	++	—	—	—	2

* In this table ♂ indicates male; ♀, female.

Seven of the patients did not show any definite signs of cardiac failure at any time, though there was a wide difference in the prominence of individual symptoms. An illustration of the type without cardiac failure is given in detail.

CASE 7 (table 13).—A girl, aged 13, became ill at the age of 5. The chief symptoms were frontal headache, vomiting, failing vision and polyuria with frequent painful urination. Recently, all symptoms became much more severe. She became practically blind, and large gray and whitish patches were seen in the retinas. The urine showed a large amount of albumin and many granular casts. Laboratory examination revealed: hemoglobin, 65 per cent.; leukocytes, 19,600, and polymorphonuclears, 87 per cent. The blood pressure was 265 systolic and 190 diastolic. The blood urea nitrogen was 107 mg. (three days before death). Postmortem examination revealed an absence of edema and fluid in the serous cavities. There was no passive congestion of the liver. The heart weighed 325 Gm. (large for body weight). There was marked ulcerative enteritis. The kidneys weighed 100 Gm. each, and had smooth surfaces and numerous small hemorrhagic and pale infarcts.

Microscopic sections showed necrosis of the small arteries with small infarcts or areas of acute atrophy and numerous necrotic arterioles (figs. 6 and 7). Some glomeruli were infarcted and others showed bands of hyaline necrosis continuous with the necrotic arteriole. A few glomeruli showed definite inflammatory changes (exudation and proliferation). There was severe sclerosis of the aorta and its large branches, but not much change in the larger branches of the renal arteries within the parenchyma.

One patient of this group with chronic hypertension presented a typical case of myocardial insufficiency for a long time but finally died of acute uremia following a cold. The history of this case follows.

CASE 19.—A man, aged 43 years, was admitted to the hospital, Aug. 22, 1922. The first symptoms began two years before admission with severe headaches. One year before admission, the headaches recurred and persisted. Nocturia, weakness and loss of weight were present for six months. He complained of epigastric pain, headache, weakness, palpitation, dyspnea and epistaxis. The heart was slightly enlarged on percussion; a systolic murmur was heard at the apex, and the rate was 120. Cyanosis was noted. The liver was felt 3 cm. below the costal margin. The blood pressure was 270 systolic and 145 diastolic. Edema was not present. The blood urea nitrogen and creatinine were within normal limits. The cardiac decompensation improved, and the patient was discharged on Sept. 9, 1922, so much better that he was able to go back to work. About two weeks later, he contracted a severe cold and shortly afterward developed dyspnea, cough, orthopnea and edema of the ankles. He was readmitted to the hospital on October 5 with all his former symptoms intensified. Slight edema of the legs and ankles was noted. The blood pressure was 245 systolic and 145 diastolic. Heavy albuminuria and many casts and a trace of phenolsulphonphthalein were found. The blood urea nitrogen was 106.4 mg.; and creatinine, 6.9 mg. Death occurred Oct. 24, 1922.

Postmortem examination did not reveal edema. The heart weighed 500 Gm. A slight passive congestion of the liver was noted. The kidneys weighed 150 Gm. each and showed finely granular surfaces and extensive acute atrophy of the tubules (fig. 8). Severe arteriolosclerosis was present with partial or complete

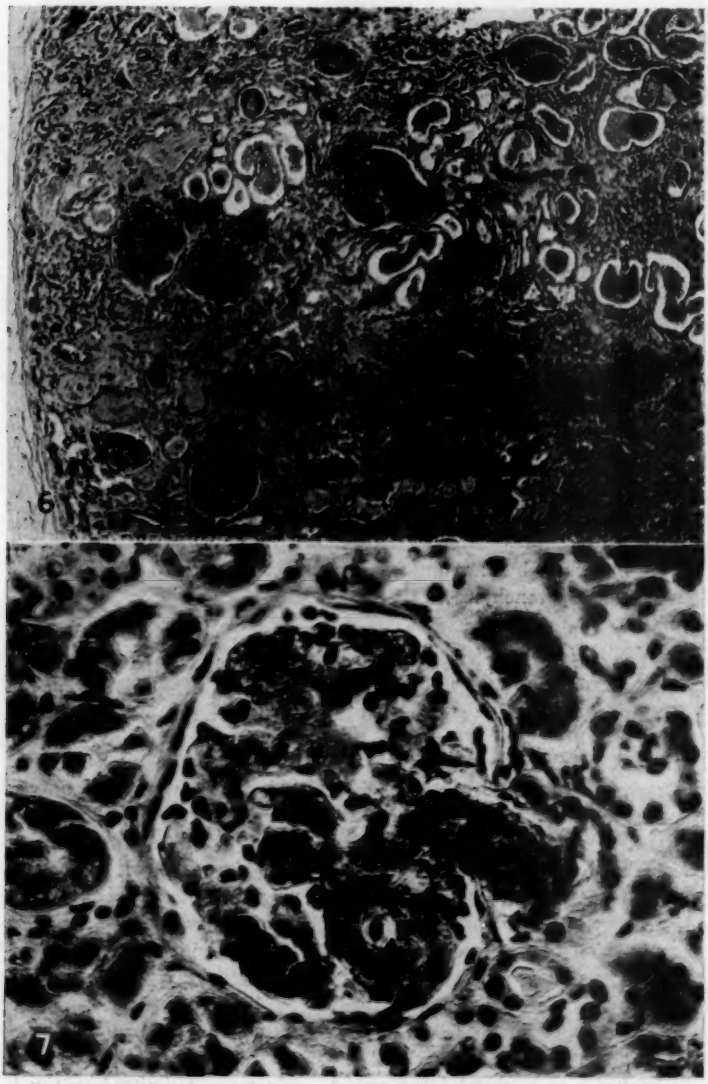


Fig. 6 (case 7, table 13).—Low magnification of area of cortex showing necrosis of arterioles with acute degeneration of tubules and glomeruli.

Fig. 7 (case 7, table 13).—Necrotic arteriole with extensions of hyaline necrosis into the glomerulus.

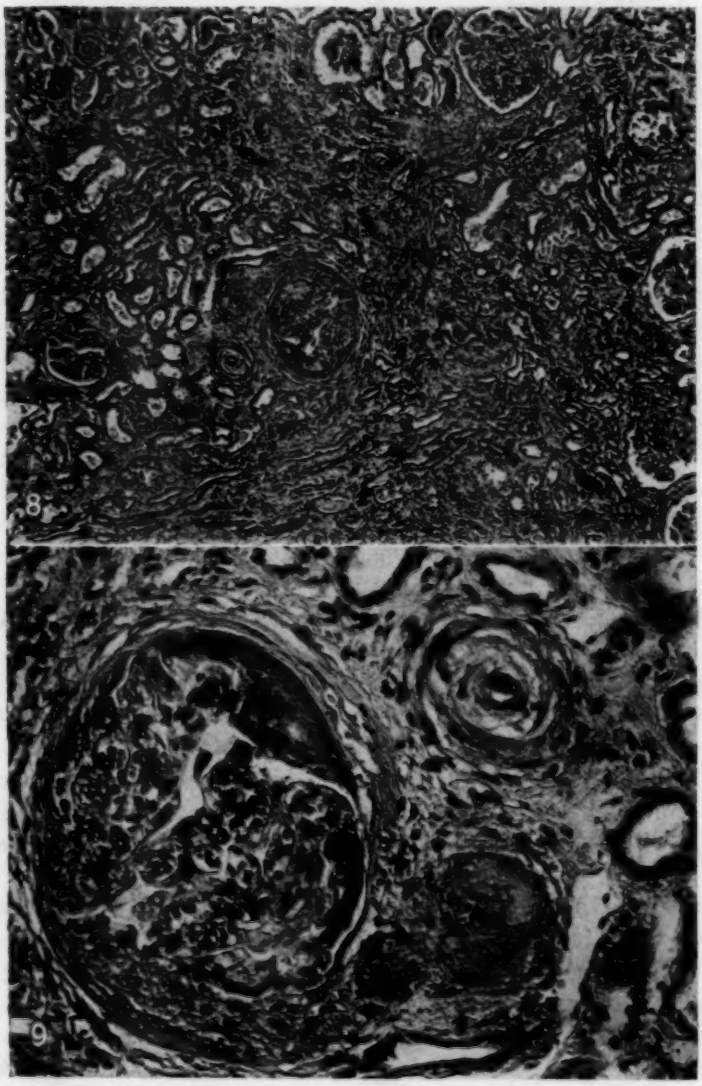


Fig. 8 (case 19, table 13).—Acute atrophy of the cortex from rapid occlusion of small arteries and arterioles.

Fig. 9 (case 19, table 13).—Necrosis of an arteriole with beginning infarction of glomerulus and acute exudative glomerulitis (many polymorphonuclear leukocytes in capillaries).

necrosis of many afferent glomerular arterioles (fig. 9) and infarction of glomeruli. A number of glomeruli showed acute glomerulitis (crescents, polymorphonuclear leukocytes and endothelial proliferation).

Type 3: Chronic Hypertension with Chronic Uremia: This is the commonest form of hypertension that is associated with uremia and includes twenty-seven of the thirty-six cases. In five cases there was a long clinical course of myocardial insufficiency. Three were complicated by cerebral hemorrhage, two by encephalomalacia, two by diabetes, one by hydronephrosis and one by bronchopneumonia. The clinical course of the twenty-seven cases was much less violent than that of the other nine, and the majority of them would not be called "malignant" by clinicians who make this diagnosis.

The average age of persons who died of "hypertension with uremia" is somewhat lower than that of persons in the other groups (fig. 3), as has been emphasized by Fahr; but this form is by no means restricted to younger persons (Herxheimer). Twenty-one of our thirty-six patients were over 50 years old. In ten of thirty-nine patients under 40 years of age, the hypertension was of the renal type. By decades, the distribution was as follows: from 10 to 20 years, two of a total of three cases were of the renal type; from 21 to 30 years, one of eight cases; from 31 to 40, seven of twenty-eight cases. The renal cases, therefore, comprise about 25 per cent of all cases of hypertension in patients under 40 years of age, but only 6.8 per cent of those in patients over 40.

Benign and malignant hypertension. Fahr distinguishes a benign form (hypertension without renal insufficiency) from a malignant form (hypertension with renal insufficiency). He was of the opinion that the two forms may be distinguished anatomically and that they differ in etiology. The benign group apparently corresponds to our four groups, namely: group I, myocardial insufficiency; group II, coronary sclerosis; group III, the encephalic group, and group IV, the miscellaneous group; the malignant form corresponds to our renal group. Fahr considers benign hypertension a simple arteriolosclerosis of the kidneys, and apparently believes that this form never ends in renal insufficiency. Malignant hypertension occurs in younger persons, ends in uremia, and anatomically shows inflammation of the afferent glomerular arterioles (arteriolitis) or glomerulitis, as well as arteriolosclerosis. He believes that malignant hypertension is due to a poison which acts directly on the arterioles and glomeruli.

Löhlein recognizes Fahr's two groups but considers them fundamentally the same disease, differing only in the speed at which the process develops and the intensity that it finally attains. Herxheimer disagrees with Fahr on the sharp separation of benign and malignant groups, and also finds that the severe form is not limited to younger

persons. The structural changes in the kidneys are described by Herxheimer and Stern as necrosis of the afferent glomerular arterioles (Arteriolonekrose) and not as arteriolitis. These investigators therefore believe with Fahr that severe cases of hypertension show a histologic structure in the kidneys different from the ordinary forms, but they do not consider it an inflammatory change and are not insistent that it is a separate entity from other forms of hypertension.

Volhard recognizes three types of hypertension: (1) a benign or stationary sclerosis without a tendency to become renal, (2) an advanced sclerosis of long duration which as a result of pure atrophy passes into renal insufficiency and (3) a rapid sclerosis which soon reaches the ischemic end-stage. In the rapid form, he thinks an inflammatory element is added to the process, and that it is not merely a difference in degree or tempo, as Löhlein believes. He admits that benign sclerosis may develop into the malignant type.

It is obvious that Fahr himself has difficulty in making a sharp separation between his two groups, since he now recognizes "borderline cases" and cases of "decompensated benign hypertension," the latter expression referring to benign hypertension with some evidence of renal damage.

Our histologic studies (table 12) show that there are innumerable degrees of anatomic damage in hypertensive kidneys. When the greater part of the kidney tissue is destroyed, signs of renal insufficiency develop, but the kidneys affected by renal insufficiency usually differ from the others only in the extent of destruction of tissue. In those cases in which uremia develops acutely (nine cases in our series), however, a somewhat different histologic picture is seen; namely, complete and rapid occlusion of the afferent arterioles with necrosis of their walls and infarction of glomeruli. In four instances, acute inflammatory changes were seen in a few glomeruli. Besides the inflammatory changes, the process may be interpreted as a severe acute arteriolosclerosis. The glomerulitis must be considered a terminal acute infection.

The thirty-six cases of the renal group are analyzed in table 13 with respect to certain microscopic structural changes in the kidneys. Cortical atrophy may be due to closure of small arteries, which results in cone-shaped areas of atrophy having the shape of infarcts; or it may be due to closure of afferent glomerular arterioles, which results in atrophy of the corresponding glomeruli and their associated tubules. Both forms of atrophy are always present, but usually one type predominates. In table 13, it appears that atrophy was caused chiefly by closure of arteries in thirteen cases and of arterioles in nine. In fourteen cases, the two types were equally prominent.

In nine cases there was evidence of a recent rapid closure of small arteries or arterioles, which is shown by necrotic arterioles leading to

infarcted glomeruli or necrotic arteries leading to infarcts or to wedge-shaped areas of acute atrophy. Clinically, these are cases that ended acutely in uremia.

In two of the nine acute cases as well as in two others that were not acute clinically, acute inflammatory changes were found in a few glomeruli. The appearance was the same as that in glomerulonephritis; there were endothelial proliferation with closure of capillaries, polymorphonuclear leukocytes and crescents, but only a few glomeruli were involved. The condition was not a diffuse glomerulonephritis.

In nine cases, some of the glomeruli showed hyaline areas continuous with the hyaline of the arteries such as those described by Löhlein (figs. 10 and 11). The appearance differed from the simple ischemic atrophy in that the glomerulus was large and only partly hyalinized. This lesion was most pronounced in the two cases of diabetes. Only one of the nine cases was clinically acute.

Our conception of the structural changes in "hypertension with renal insufficiency" is as follows: When uremia comes on slowly, the change is a pure ischemic atrophy from progressive narrowing of small arteries and arterioles. This is the usual form (twenty-seven of thirty-six cases). When uremia develops rapidly, acute necrosis of the arteries and arterioles is found, often with small infarcts or infarcted glomeruli. Rarely, there is some glomerulitis. The rapid development of uremia in case 19 following a severe cold suggests that acute infection may sometimes hasten the closure of arterioles and bring on uremia more rapidly. Infection may sometimes play a rôle in the development of "hypertension with acute uremia," but in three fourths of our cases of "hypertension with uremia," there was no suggestion of infection.

The expression "malignant" might be appropriately applied to our nine cases of hypertension with acute uremia, since the course was rapid and stormy, but it is ill adapted to describe all cases of hypertension with uremia. It is not clear why a disease ending in uremia should be called malignant while one ending in myocardial exhaustion or apoplexy is called benign. Some American clinicians have adopted the expression "malignant hypertension," but they use it to denote a serious prognosis rather than a renal involvement.

GROUP V.—*Miscellaneous Group.*—This group includes persons who died from accidental injuries or intercurrent diseases. Fifteen deaths resulted from accidental injuries. The intercurrent diseases were carcinoma, five cases; carbon monoxide poisoning, two; undetermined poison, two; lobar pneumonia, four; bronchopneumonia, two; diabetic gangrene, two; septicemia, three; postoperative complications, six; cirrhosis of the liver, one; leukemia, one; pernicious anemia, one; acute cholecystitis, one; duodenal ulcer with hemorrhage, one; diabetic coma,

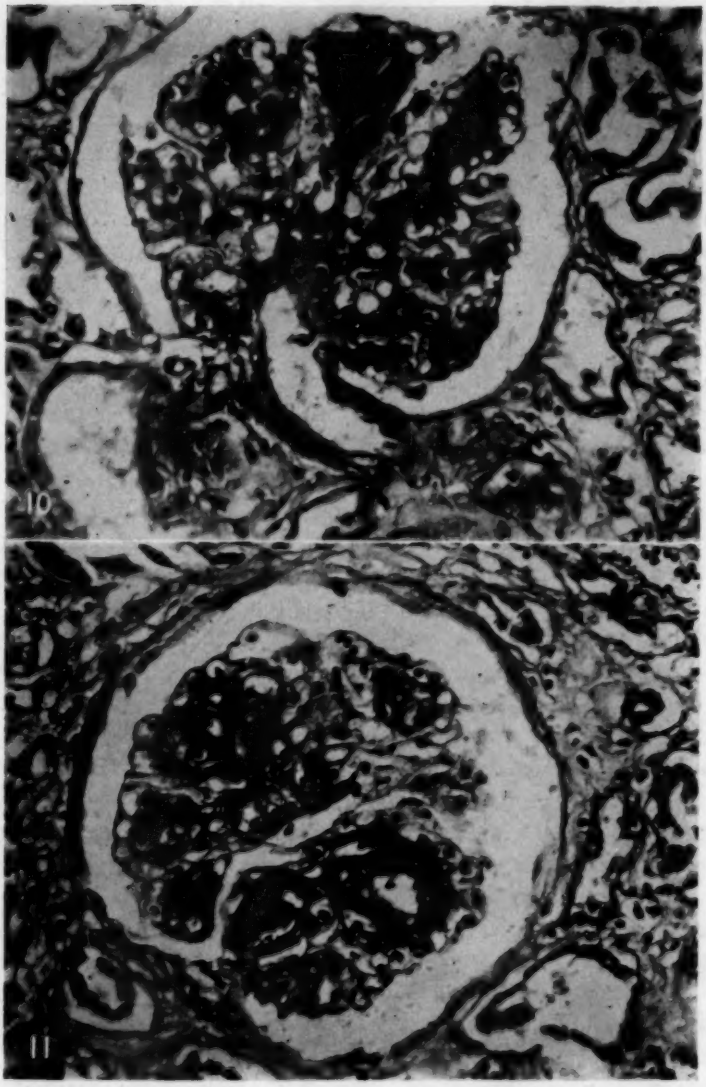


Fig. 10.—Hyaline degeneration in wall of arteriole continuous with compact areas of swollen endothelium in the glomerulus. These compact areas soon become hyalin. See figure 11.

Fig. 11.—Same case as figure 10. The areas of swollen endothelium have become partly hyalinized.

one, and in two cases the intercurrent disease was undetermined. One disease conspicuously absent in all cases of hypertension is tuberculosis. Minor calls attention to the rarity of cases of hypertension in hospitals for the tuberculous.

The predominance of males in this group is no doubt due to the preponderance of males in the coroner's service.

Only four of this group were known to have had high blood pressure. With a few exceptions, they were not experiencing serious discomfort from this disease. They may be considered examples of the earlier stages of hypertension. There is less renal arteriolosclerosis in this group than in any other except the coronary group.

RENAL ARTERIES IN HYPERTENSION

According to Jores, the internal elastic lamina of the renal arteries is a single layer in childhood, but with increasing age it splits at first into two layers and finally into three or more. In advanced life, therefore, there is regularly a definite thickening of the intima, largely due to increase in elastic tissue (elastic-hyperplastic intimal thickening). Both Wallgren and Oppenheim find the same age changes in the intima that were described by Jores, but the former considers the newly formed elastic layers as separately differentiated and not split off from the original layer. Friedemann calls attention to the marked hyperplastic-elastic intimal thickening that occurs in cases of primary hypertension, and interprets it as a compensatory hypertrophy in response to the increased intravascular pressure.

As far as our observations go, the renal arteries show this elastic intimal thickening much more prominently than arteries elsewhere. It increases gradually with age and is much more pronounced in relation to long continued high blood pressure. Beyond a certain degree, it begins to narrow the lumen of the vessel and cause atrophy of cone-shaped areas of the cortex. It is seldom absent in the kidneys of elderly persons, and only marked intimal thickening of this type can be considered indicative of hypertension. Some pathologists have expressed the opinion that elastic intimal thickening is not true arteriosclerosis, since it begins so early in life; but the same argument would apply to atheroma, which every one considers a pathologic change. Like atheroma, it does not cause a functional disturbance until it begins to produce narrowing of an artery. Elastic-intimal thickening may extend as far as the afferent glomerular arterioles, but it does not involve these vessels. It is interpreted as a senile change unless of severe degree, in which case it indicates hypertension.

As the intima thickens the media gradually undergoes atrophy, usually in an uneven way, the thin parts corresponding to specially

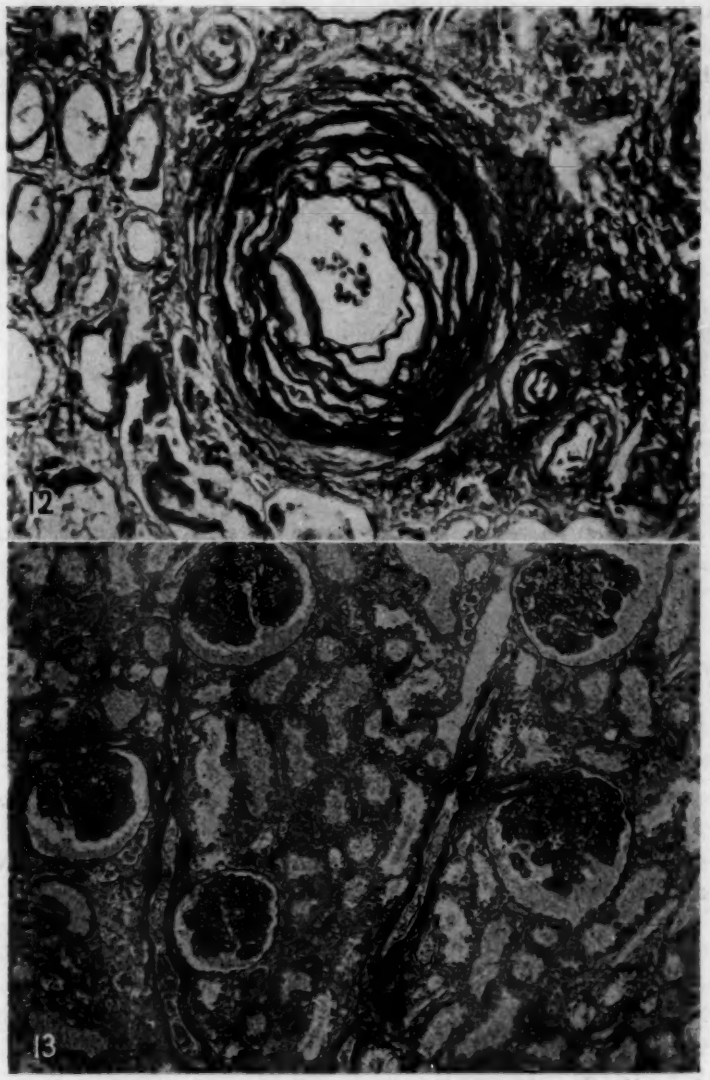


Fig. 12.—Transverse section of a small renal artery showing hyperplastic-elastic intimal thickening. Elastic tissue stain. Elastic lamellae are stained black. Note the thickened intima containing many elastic lamellae, and the atrophy of the media.

Fig. 13.—Arteriolosclerosis. Arterioles in longitudinal sections showing an uneven layer of subendothelial hyalin. No marked narrowing of arterioles. No atrophy.

thickened parts of the intima. The artery changes from its normal muscular type to the elastic type characteristic of large arteries like the carotid (fig. 12).

The larger renal arteries often show a typical atherosclerosis with lipoid infiltration.

The degree of sclerosis of the renal arteries in hypertension is shown in table 14. It will be noted that it is present in some degree in 97.6 per cent of the persons examined. We have not made a study of its occurrence in nonhypertensive cases.

Jores finds hyperplastic-elastic intimal thickening in the small arteries of the spleen, pancreas and brain in cases of "nephritis." Such changes were rare in the stomach, intestines and liver, and were not found in the skeletal muscles.

TABLE 14.—*Sclerosis of Renal Arteries*

	Myocardial	Coronary	Apoplexy	Renal	Miscellaneous	Total
None	3.2%	3.1%	1.5%	0	2 %	2.4%
Slight to moderate	36.9%	50.8%	20.5%	8.3%	45.8%	35.8%
Severe	59.8%	46 %	72 %	91.7%	52.2%	61.7%
Number of cases examined	157	63	64	36	48	368

TABLE 15.—*Renal Arteriolosclerosis*

Degree	Myocardial Insufficiency	Coronary Disease	Encephalic Group	Renal Insufficiency	Miscellaneous	Total
None	7.6%	17.5%	9.3%	0	20.8%	10.6%
Slight to moderate	52.9%	55.5%	28.1%	11.1%	50 %	44.5%
Severe	39.5%	27 %	62.5%	88.9%	29.2%	44.8%
Number examined	157	63	64	33	48	368

ARTERIOLES IN HYPERTENSION

The term "arteriole" is commonly used to designate small precapillary vessels composed of muscle and endothelium with little or no other tissue. We have used it, so far as our own observations on the kidney are concerned, to include only the afferent and efferent glomerular vessels, but some writers evidently include larger arteries. When one speaks of arteriolosclerosis, it is important to know just what vessels are meant, since the ordinary senile changes often extend as far as the afferent glomerular arterioles. Those who use "arteriole" in the broader sense find a higher percentage of arteriolosclerosis in hypertensive kidneys than those who restrict it to the afferent and efferent glomerular vessels. The incidence of arteriolosclerosis in the several forms of hypertension is shown in table 15.

It will be noted that 10.6 per cent of the kidneys examined did not show arteriolosclerosis, and that the percentage without arteriolosclerosis is much greater in the coronary and miscellaneous groups.

A thickening of the renal arterioles in chronic interstitial nephritis was recognized by Bright. Gull and Sutton first recognized generalized arteriolar narrowing in this condition, and call it arteriocapillary fibrosis. This is not an appropriate term, since the capillaries do not show structural changes. Gull and Sutton evidently include under the heading chronic interstitial nephritis many cases in which the kidneys are affected by ordinary senile changes (small areas of atrophy from sclerosis of arteries) as well as by glomerulonephritis and by arteriolosclerosis.

Ziegler first distinguished the arteriosclerotic kidney sharply from other forms of contracted kidney and recognized changes in the arterioles as well as in the large arteries. He seems to believe that there are transitions between the senile kidney and the clinical types. Gaskell describes narrowing of the afferent glomerular arteries as a cause of glomerular atrophy in the vascular type of nephritis. Herxheimer describes arteriolosclerosis of the kidneys in ten cases of hypertension. Similar arteriolar changes were noted in the pancreas, but they were less pronounced except in some cases of diabetes in which they were prominent. Löhlein gives excellent illustrations of arteriolosclerosis showing the extension of the hyaline layer from the arteriole into the glomerulus. Fahr writes extensively concerning the sclerosis of renal vessels. He finds that small arteries of the pancreas also are usually sclerotic in cases of hypertension (in forty-four cases, six with normal vessels, thirteen with slight and twenty-five with moderate or severe sclerosis), but that there is rarely any involvement of the small arteries of the skin, skeletal muscles or intestines. He believes that a marked sclerosis of the renal vessels is always associated with cardiac hypertrophy unless some factor such as cachexia interferes with the enlargement of the heart. Watanabe, in a study of 116 cases of generalized arteriosclerosis, finds only six in which there was sclerosis of the small arteries of the cutis.

In a study of seventy-two cases of hypertension histologically, Fishberg finds renal arteriolosclerosis in 100 per cent. However, he apparently includes as arterioles vessels larger than the afferent glomerular vessels, a circumstance which would explain his remarkably high percentage of arteriolosclerosis. He finds arteriolosclerosis in the various organs as follows: in the kidney, in each of the seventy-two cases; in the spleen, in forty-five of sixty-eight; in the pancreas, in twenty-three of sixty-eight; in the liver, in twenty-one of seventy; in the suprarenals, in seventeen of fifty-nine; in the brain, in six of thirty-one; in the gastro-intestinal tract, in three of thirty-four; in the heart, in two of sixty-eight; in the lung, in none of seventy; in the voluntary muscles, in none (number of observations not given).

We have not made statistical studies of arteriolosclerosis in any organ except the kidney, but our impressions from the examination of a

great many sections of the spleen, pancreas and liver correspond with Fishberg's statistics.

Arteriolosclerosis in Relation to Hypertension.—Does renal arteriolosclerosis occur independently of hypertension? Both Wallgren and Oppenheim describe small hyaline droplets in the afferent glomerular arterioles in cases in which they believe that hypertension has been excluded. Fishberg also believes that a slight arteriolosclerosis may be found in the absence of hypertension.

Our own studies do not enable us to answer this question satisfactorily. On our records there are a number of cases of arteriolosclerosis associated with hearts of normal weight; but in every such instance in which the blood pressure was read it was found to be high, unless there was some associated condition which tends to lower blood pressure, such as coronary disease, cardiac decompensation or impending death. No instances of definite sclerosis of the afferent glomerular arterioles were observed in which hypertension could be excluded with certainty, so that we are inclined to consider this lesion pathognomonic of hypertension; but further studies should be made before we conclude that this relationship is without exceptions.

Sclerosis of the vessels from which the afferent glomerular arterioles arise is often observed in nonhypertensive cases.

Is renal arteriolosclerosis always present in cases of hypertension? Fishberg did not find any exceptions in his seventy-two cases; but it has already been pointed out that he apparently includes as arterioles somewhat larger vessels than we have in mind. Von Monakow, Fahr and various other authors mention cases of hypertension in which the kidneys were normal, but it is not clear from their reports that the arterioles were carefully examined. Kidneys with definite arteriolosclerosis may appear entirely normal on gross examination. Our tables show that of 368 cases in which microscopic examination was performed, thirty-nine (10.6 per cent) did not show renal arteriolosclerosis.

High blood pressure (average 176 mm. of mercury) was known to have been present in fifteen of the thirty-nine, and the hearts ranged in size from 365 Gm. to 770 Gm. (average 515 Gm.). They were all typical clinical examples of hypertension. In the group of twenty-four cases in which the blood pressure was not known, the average weight of the heart was 558 Gm., and the extremes 490 and 760. Fifteen of these were also clinical examples of hypertension. Accidental death had occurred in nine.

Some of the other organs in the thirty-nine cases referred to were examined microscopically for arteriolosclerosis. The results were as follows: spleen, 12 +, 7 —; pancreas, 4 +, 7 —; liver, 1 +, 13 —; lung, 16 —; heart, 15 —; brain, 1 +, 3 —.

Our observations indicate that anatomic changes may be demonstrated in the afferent glomerular arterioles in 90 per cent of persons that have primary hypertension, and that the small renal arteries are rarely normal in this disease. But undoubted cases of hypertension do occur in which the afferent glomerular arterioles do not show anatomic changes.

Arteriolosclerosis is also found in organs other than the kidneys in hypertension. Arteriolosclerosis of the spleen is usually found in cases of hypertension, but it occurs also in a large majority of elderly persons (Herxheimer) without relation to hypertension. It is improbable, therefore, that there is any close relationship between disease of the splenic arterioles and hypertension.

The arterioles of the pancreas are frequently diseased in hypertension (Fahr, Fishberg), but there are no published studies on the incidence of this condition in the pancreas in nonhypertensive cases. The relationship of pancreatic arteriolosclerosis to hypertension, therefore, is incompletely known.

The arterioles of the brain are sometimes diseased in cases of hypertension (Gull and Sutton, Fishberg, Bordley and Baker, Evans), but the observations recorded are too few to justify any conclusions. Much more work is needed to determine the frequency of arteriolosclerosis in the brain in hypertensive and in nonhypertensive cases.

As regards arteriolosclerosis of the skin, muscles and gastro-intestinal tract, several observers agree that it is uncommon (Watanabe, Fahr, Fishberg). The arterioles of the heart muscle and the lungs are likewise not affected in cases of hypertension (Evans, Fishberg).

There is abundant clinical evidence that the small arteries of the retina are usually diseased in cases of hypertension (O'Hare and Walker), but more histologic studies of the retina are needed. In the three cases in which we made a microscopic study definite arteriolosclerosis was present.

Sufficient studies are available to show that generalized arteriolosclerosis does not occur in cases of hypertension. The part of the arteriolar system that is organically narrowed is relatively small, even in the most extreme cases, so that a case of hypertension cannot be explained on the purely anatomic basis of organic arteriolar disease. One must believe that increased tonicity of the arterioles is chiefly responsible for the increased peripheral resistance.

STRUCTURAL CHANGES IN THE RENAL ARTERIOLES

Löhlein considers dilatation of the afferent glomerular arteriole near its entrance into the glomerulus as the earliest anatomic change in hypertension. Jaffe holds the same view. We have rarely observed dilatation of this arteriole in our material, and therefore we do not

agree that it is of constant occurrence. The first change that we have observed is a thin layer of hyaline material immediately under the endothelium (fig. 13). This increases in amount as the disease advances. It is deposited unevenly, as may be seen in longitudinal sections, and the thicker hyaline deposits correspond to areas of greater thinning of the media. At first the hyaline layer may not completely encircle the lumen of the vessel. In cases of slight or moderate sclerosis, the hyaline deposit is usually more pronounced in the proximal than in the distal part of the arteriole; i. e., the portion adjacent to the glomerulus is usually involved somewhat later than the part near the origin from the larger vessel. Small deposits of hyalin appear to lie

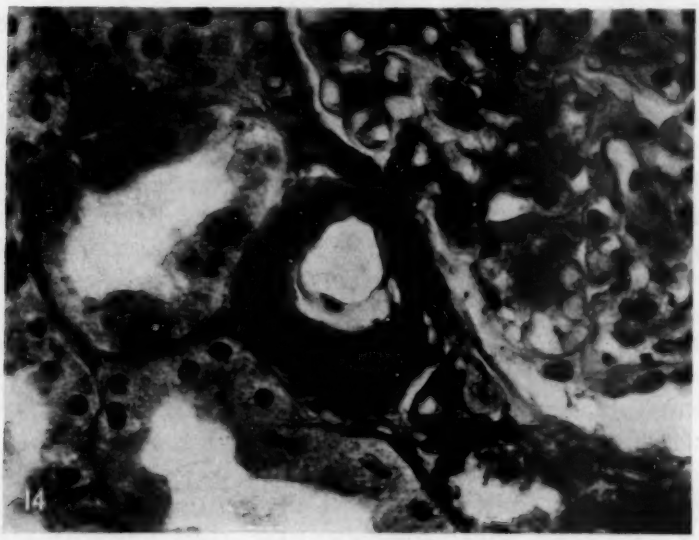


Fig. 14.—Transverse section of an arteriole showing replacement of the muscle by hyaline material. From a case of diabetes.

definitely between the endothelium and the muscle layer, and sometimes larger deposits similarly displace the muscle outward; but often the muscle layer is infiltrated or directly transformed into hyaline material (fig. 14). The hyaline material is commonly much more abundant in elderly diabetic than in nondiabetic persons.

There is never any disease of the afferent glomerular arterioles when the small arteries of the kidney are entirely normal; but the latter vessels are frequently found diseased when the afferent glomerular arterioles are normal. There is abundant evidence that disease of the larger vessels precedes that in the terminal arterioles, except in some of the cases of acute hypertension with uremia already described, in which the arteriolar lesions are more severe than those in the arteries.

The chemical composition of the hyaline substance has not been determined. Hueck considers it a combination of various coagulated albuminous bodies. Some investigators believe that it is filtered through the endothelium into the wall of the vessel. This explanation may be satisfactory for subendothelial deposits; often, however, the muscle fibers do not atrophy, but appear to be infiltrated by and transformed into hyalin.

There is never a true arteritis, i. e., a leukocytic infiltration of the wall such as may occur in glomerulonephritis. The change is more aptly called hyalinization or sclerosis. Hueck, Munk and others maintain that moderate deposits of hyalin do not increase the resistance to the flow of blood, since the lumen is not necessarily narrowed in the early stages and since there is no satisfactory evidence that hyalin is a rigid substance. But any subendothelial deposit must narrow the lumen to some extent unless there is a compensatory dilatation and it seems probable that it would also interfere with the free contraction and relaxation of the arterioles, which might increase resistance. Extensive deposits of hyalin undoubtedly narrow the lumen of the arteriole and interfere greatly with the power of the circular muscle to regulate its caliber.

In cases of acute hypertension that end acutely in uremia, a rapid necrosis of the arteriole with closure of its lumen often occurs (figs. 5 and 7). The closure may develop so rapidly that infarction of the glomerulus is produced (fig. 5). The wall of the arteriole swells and undergoes necrosis. Relatively little thrombotic material is formed. Some cases of either acute or chronic type show an extension of the hyaline degeneration from the arteriole into the glomerulus (figs. 7, 10 and 11). Compact masses of swollen endothelial cells appear around the capillaries and later undergo hyaline degeneration. The changes in the glomeruli are of four types:

(*a*) *Simple Atrophy from Reduced Blood Supply.*—Atrophy is by far the most common change in all types except the cases of hypertension that terminate acutely in uremia. The glomerulus decreases slowly in size until its diameter is about half that of the normal, its histologic structure disappears and it assumes a homogeneous hyaline appearance. Simple atrophy is always due to either hyaline degeneration and occlusion of the afferent arteriole or hyperplastic intimal thickening of a small artery. Narrowing and closure of small arteries is a frequent cause of atrophy in groups of glomeruli and tubules. Frequently glomeruli whose afferent arterioles arise directly from larger arteries atrophy earlier than those whose arterioles come from terminal arteries This is due to the closure of the arterioles at their origins by the greatly thickened intima of the larger vessels.

(*b*) *Rapid Hyalinization of the Glomerulus.*—Hyalinization of the glomerulus is frequently seen in diabetic persons. The hyaline degeneration may extend directly from the arteriole into the endothelium of the glomerulus. The glomerulus becomes hyalin before any decrease in size occurs; in fact, there may be some preliminary swelling of the endothelium.

(*c*) *Infarction of the Glomerulus.*—Infarction occurs in certain cases that progress rapidly to a fatal uremia, and is due to necrosis of the arteriole with a rapid closure of its lumen.

(*d*) *Terminal Acute Glomerulitis.*—In a case with hypertension, a terminal glomerulitis rarely develops from an infection. The lesion does not resemble diffuse glomerulonephritis closely, since it is focal rather than diffuse, but there are crescents, proliferation, swelling of the endothelium and an increased number of leukocytes.

The majority of persons who have symptoms caused by hypertension have albumin in the urine from time to time. Albuminuria is especially noticeable in the myocardial and renal types. Passive congestion of the kidneys is perhaps the commonest cause; but it is often found in the absence of cardiac decompensation, in which instances it may be interpreted as being due to injury of the glomerular endothelium by anemia. There is generally a marked decrease of albumin when the heart recovers compensation. Albuminuria is by no means an indication of serious renal involvement in cases of primary hypertension, and the amount of albumin in the urine does not bear any direct relation to the extent of renal damage.

WEIGHT OF HEART

The weight of the heart in the various groups and subgroups is shown in table 4. The average weight of the heart in the group with myocardial insufficiency is definitely greater than that of the other groups. It will be noted that in each of the three subgroups *A*, namely, those in which it was known that the blood pressure was high, there are a number of hearts below the 450 Gm. and 500 Gm. limits. Death may ensue before the heart becomes large. This seems to be especially true in the encephalic and renal groups. It is obvious, therefore, that we have excluded a number of cases of hypertension from the encephalic, coronary and miscellaneous groups in which the blood pressure was unknown and in which the weight of the heart was below the arbitrary limits that we have used.

The weight of the heart in a case of hypertension depends on several factors: 1. The degree of the increased peripheral resistance. It is obvious that less work is required to force the blood through arterioles that are only slightly narrowed than through those that are markedly narrowed. Spastic is apparently more important than organic

narrowing of arterioles. Arteriolosclerosis occurs much more frequently in the kidney than in other organs, but there is no definite relation between the weight of the heart and the degree of renal arteriolosclerosis. In 39 of 368 cases arteriolosclerosis was not found in the kidneys, but the average weight of the hearts was 545 Gm. Some of the largest hearts were associated with normal appearing renal arterioles. The blood pressure may be taken as a measure of the work the heart is doing at any given time.

2. Duration of the increased peripheral resistance. This is an important factor. It is known that with the exception of advanced cases, the blood pressure usually drops from 30 to 60 mm. of mercury during sleep. Many persons have intermittent hypertension. Great variations are often found when the pressure is read every few minutes for an hour or more (Kaufmann). These facts may explain why occasionally a patient with hypertension of ten years' duration has a heart weighing less than 500 Gm. We can also understand why in a case of only three months' duration the heart may weigh 350 Gm., although the blood pressure has been constantly above 250 mm. of mercury.

3. The ability of the myocardium to undergo compensatory hypertrophy. This depends on the condition of the coronary arteries and the age and general nutritive condition of the individual. Disease of the coronary arteries decreases the blood supply of the myocardium and tends to prevent hypertrophy.

The weight of the heart in a given case of hypertension, therefore, depends on the degree and duration of the peripheral resistance and the nutrition of the myocardium.

THE RELATION OF ARTERIOSCLEROSIS TO ARTERIOLOSCLEROSIS AND HYPERTENSION

Are these distinct types of arterial disease or are they the same disease differing only in the size of the vessels affected? This question cannot be answered satisfactorily at present, but the lines of investigation which have been undertaken to solve the problem will be discussed. Hypertension and arteriolosclerosis will be considered together, since they correspond in 90 per cent of cases.

1. *Structure of the Lesions.*—Arteriosclerosis is a collective term used to designate several anatomic forms of arterial disease that may or may not be related. Formerly syphilitic arteries and thrombo-angiitis obliterans were included. (*a*) Intimal atherosclerosis is the main type in the aorta, the carotids and the coronaries and may be found in any artery. It is characterized by proliferation of the connective tissue of the intima with edema, lipoid infiltration, necrosis and calcification of

the newly formed tissue. It increases progressively with age, but some elderly persons show little. A juvenile form occurs which is usually associated with arteriolosclerosis and hypertension. It is more severe in elderly persons with diabetes than in persons of the same age without diabetes. A condition resembling intimal atherosclerosis may be produced in animals by prolonged feeding of diets rich in cholesterol.

(*b*) Calcification of the media is a widespread condition (Mönckeberg, Faber). It is found in the pelvic, gluteal and popliteal arteries of children. It tends to increase with age. It is more frequent and extensive in the arteries of the pelvis and lower extremities, but is also found in many other arteries (e. g., descending aorta, subclavian, superior mesenteric, etc., Faber). It is rare in the coronary and renal arteries.

(*c*) Hyperplastic-elastic intimal thickening occurs chiefly in the small muscular arteries, especially in those of the kidneys. The increase in the thickness of the intima is mainly due to newly formed layers of elastic tissue. This type begins in early adult life and also increases progressively with age. Degenerative changes of atheromatous type may be superimposed. Elastic intimal thickening is much more pronounced in association with prolonged hypertension.

(*d*) Senile ectasia occurs in the aorta and in the large arteries of elastic type. There is degeneration of the elastic tissue with numerous ruptures of the lamellae, which results in dilatation of the vessel with thinning of its wall and loss of elasticity. Intimal atherosclerosis is usually not conspicuous in this form.

(*e*) Regenerative intimal thickening (Jores) occurs as a result of disuse, e. g., after ligature of a vessel, in an artery supplying an organ such as the uterus in the process of involution, or in an artery supplying an area of atrophy, e. g., in the kidney in glomerulonephritis. The intimal thickening is due to the formation of delicate fibrous tissue. It does not contain coarse elastic lamellae as in type *c*.

It is unusual to find either atherosclerosis or medial calcification of severe degree in the pulmonary arteries. The coronary arteries seldom show any form except intimal atherosclerosis. The renal arteries show chiefly hyperplastic-elastic intimal thickening, sometimes atherosclerosis and regenerative intimal thickening, rarely medial calcification. The arteries of the lower extremities show both medial calcification and intimal atherosclerosis.

In the arterioles of small size such as the afferent glomerular vessels the only changes are a subendothelial deposit of hyalin and hyalinization of the media. When the hyaline material accumulates in large amounts, it may close the lumen of the vessel partially or completely. Often it is possible to demonstrate fatty material in the hyaline material. A few

observers believe that a slight hyaline degeneration of renal arterioles occurs as a senile change. Arteriolosclerosis develops as a rule much later in life than arteriosclerosis.

It is obvious that the histologic structure of a sclerotic arteriole is different from any of the foregoing forms of arteriosclerosis; but it is no more different from intimal atherosclerosis than hyperplastic-elastic intimal thickening. In other words, a small sclerotic renal artery does not resemble the sclerotic aorta any more closely than it resembles a sclerotic arteriole. Furthermore, the absence of the intima in an arteriole precludes the development of any of the forms of intimal thickening found in arteriosclerosis, even if there is a common etiologic factor for both arteriosclerosis and arteriolosclerosis. The one factor in common between intimal atherosclerosis and arteriolosclerosis is degeneration of the wall of the vessel. The wide differences in the histologic structure of large arteries and terminal arterioles would seem to prevent any close resemblance of degenerative lesions, even though the same morbid agency acts on both. It does not seem that the microscopic structure alone justifies a fundamental distinction between arteriosclerosis and arteriolosclerosis.

2. *Distribution of the Different Forms of Arterial Disease in the Various Organs and the Relation of Each to Hypertension.*—Arterial disease often varies greatly in type and in intensity in the different organs of a person.

The vessel most commonly affected is the aorta, especially the lower part of the abdominal portion, which is seldom entirely free from disease in elderly persons. The form of disease is chiefly intimal atherosclerosis, but senile ectasia is frequently seen in the arch and medial calcification in the descending aorta. Sclerosis of the aorta does not bear close relationship to hypertension. It may be severely involved in the absence of hypertension or practically normal in association with it.

The Heart: Disease of the coronary arteries is a common form of arteriosclerosis. Brooks found these vessels diseased in 270 of 400 cases of general arteriosclerosis. The type is almost entirely intimal atherosclerosis. Calcification of the thickened intima is common. The disease is largely limited to the main trunks and their large branches, the left much oftener than the right. It seldom extends into the small coronary branches, and arteriolosclerosis is rare in the myocardium. Coronary disease is much more pronounced in hypertension than in nonhypertension. In our group of 136 cases in which death occurred from coronary disease there is satisfactory evidence that approximately 68 per cent were associated with hypertension.

The Brain: Intimal atherosclerosis of the arteries of the base of the brain is frequently observed, and ectasia is not infrequent. Hemorrhage is usually due to disease of small arteries within the substance

of the brain, but encephalomalacia results from occlusion of relatively large arteries. In our series about 90 per cent of both forms of apoplexy are associated with hypertension. Arteriolosclerosis in the brain is relatively infrequent, according to most observers, but Bordley and Baker found it in each of the fourteen cases that they examined.

The Kidneys: Intimal atherosclerosis of the main trunks of the renal arteries is not infrequent; medial calcification is rare. Hyperplastic-elastic intimal thickening of the arteries within the renal parenchyma is practically always present to some extent after middle life, and seems to be independent of intimal atherosclerosis. In our necropsy examinations, renal arteriolosclerosis was found in approximately 13.5 per cent of persons over 50 years old, and it is almost always associated with hypertension. Hyperplastic-elastic intimal thickening is much more pronounced in hypertension.

The Spleen: Atherosclerosis of the splenic artery is a common postmortem observation, but it is rarely of clinical interest. Arteriolosclerosis is seen with increasing frequency from early adult life onward (Herxheimer). A study has not been made of the relation between splenic arteriolosclerosis and disease of the splenic or other large arteries. Splenic arteriolosclerosis is largely independent of hypertension.

The Pancreas: Satisfactory studies have not been made of the pancreatic arteries and arterioles. It is known, however, that arteriolosclerosis is fairly common in cases of hypertension.

In the extremities, especially the lower ones, sclerosis of the large arteries is common. Both medial calcification and intimal atherosclerosis occur. These arteries may be severely involved when arteriosclerosis elsewhere is insignificant. Arteriolosclerosis in the muscles and skin is rare. It is known clinically that there is no close relation between hardening of the peripheral arteries and hypertension. However, the statistics from Sawada usually quoted on this point are of little value since he excluded all cases with signs of involvement of heart or kidneys, thus eliminating most of the cases of hypertension from the group. He also used 130 mm. of mercury as the dividing line between hypertension and normal blood pressure.

3. *Association of Arterial and Arteriolar Disease in Certain Forms of Hypertension.*—In some cases of hypertension in juvenile patients, in many acute cases, in elderly diabetic persons and in certain other cases, both arteries and arterioles are often extensively diseased. The lesions are continuous from the large arteries to the terminal renal arterioles, the histologic structure varying with the size of the vessel.

The foregoing evidence may be summarized as follows: There are at least five histologic varieties of lesions included in the collective term "arteriosclerosis," which differ from one another as much as they differ from arteriolosclerosis. The histologic differences between

arteriolosclerosis and some of the forms of arteriosclerosis may be due to differences in the structure of the walls or in the function of the arterioles and larger arteries rather than to dissimilarity in etiology. Certain forms of arteriosclerosis (e. g., atherosclerosis of the arteries of the brain and of the coronary arteries and hyperplastic-elastic intimal thickening of the renals) are closely related to renal arteriolosclerosis and hypertension, while other forms (e. g., sclerosis of the aorta and of the peripheral arteries) do not show any definite relationship. Therefore the common statement that "arteriosclerosis has no connection with hypertension" is incorrect. There is a striking dissimilarity in the incidence of arteriosclerosis and arteriolosclerosis in the various organs for which no explanation is offered. In certain cases, e. g., in juvenile hypertension, arteriosclerosis and arteriolosclerosis are associated in such a way as to suggest a common etiology. Renal arteriolosclerosis is nearly always associated with hyperplastic-elastic intimal thickening of the small renal arteries.

ETIOLOGY OF HYPERTENSION

The blood pressure is regulated chiefly by contraction and relaxation of the precapillary arterioles which receive their nerve supply (vasomotor fibers) from sympathetic ganglions. A vasomotor center in the medulla regulates the tonus of the vascular musculature through impulses which reach the vessels via the sympathetic fibers. Section of a sympathetic nerve is followed immediately by dilatation of the arterioles that it supplies; but after varying periods (a few weeks to a few months) the vessels usually regain their normal tonus. Stimulation of the nerve causes contraction of the arterioles. Stimulation of the vasomotor center causes general arteriolar contraction which results in increased blood pressure. There is abundant physiologic evidence that the vasomotor center may be stimulated by irritants that act directly on it or by impulses that reach it via the peripheral nerves. We may, therefore, speak of hypertension due to direct or to reflex stimulation of the vasomotor center.

Theoretically, it is possible that substances circulating in the blood may act directly on the sympathetic cells or their fibers or the smooth muscle of the arterioles, causing increased tonus and resulting in hypertension. The hypertension resulting from injections of epinephrine has been shown to be due to the direct action of this substance on the terminations of the sympathetic fibers in the smooth muscle of the arteries and arterioles. Theoretically, there may be a reflex stimulation of the arterioles through the sympathetics without involvement of the vasomotor center.

We shall now discuss the various factors that may be concerned in the etiology of hypertension.

1. *Increased Intracranial Pressure.*—Cushing devised an ingenious experiment to study the influence of intracranial pressure on blood pressure. A cannula was inserted into the subdural space through a watertight opening in the skull and connected with a beaker of normal salt solution. The intracranial pressure was varied by raising and lowering the beaker. A mercury manometer connected with the cannula registered the intracranial pressure, and by means of a carotid cannula the blood pressure was recorded simultaneously. By this method, the intracranial pressure is uniform throughout the cranial cavity. When the intracranial pressure was raised above the level of the blood pressure, a sharp rise of the latter occurred. This reaction did not occur after section of the spinal cord. Cushing explains the hypertension as due to anemia of the vasomotor center in the medulla. Localized pressure on parts of the brain produced by introduction of solid material usually did not cause a rise of blood pressure. Cushing considers that solid bodies did not cause a uniform increase of intracranial pressure and therefore usually no increased pressure on the medulla.

In the case of intracranial hemorrhage, although the blood pressure is usually abnormally high prior to the stroke, it is occasionally observed to rise even higher immediately afterward. In one such case which we examined post mortem there was a large quantity of fluid blood surrounding the entire brain and thus causing uniformly increased pressure, as in Cushing's experiment with fluid. In the majority of instances of intracranial hemorrhage, the mass of blood is found in a localized area, so that it has the effect of a solid and does not exert much pressure on the medulla. This circumstance may explain the fact that intracranial hemorrhage so commonly does not cause a rise of blood pressure. The same explanation is offered for the absence of hypertension with tumors of the brain.

In some cases of primary hypertension, the cerebrospinal fluid is under increased pressure and the blood pressure falls somewhat after lumbar puncture (Kahler); but there is no satisfactory evidence that increased intracranial pressure is a cause of primary hypertension.

Burton-Opitz and Edwards believe that they have shown that there is an increased flow of blood through the brain before and during the experimental increase of intracranial pressure in Cushing's experiment, and that therefore anemia of the vasomotor center is not the cause of this form of hypertension.

2. *Sclerosis of the Arteries and Arterioles of the Medulla.*—Since anemia of the vasomotor center resulting from increased intracranial pressure causes hypertension, it has been inferred that anemia from arteriosclerosis might act in the same way. Riebold reports a case of primary hypertension with marked sclerosis of the arteries of the brain which he considered the cause of the high blood pressure. Fahr believes

that some cases of hypertension are due to disease of the arteries of the brain. Lippmann finds sclerosis of medium-sized and small arteries in 80 per cent of the cases of primary hypertension. Bordley and Baker finds arteriolosclerosis of the vessels of the medulla in each of fourteen cases of primary hypertension in which they made microscopic studies. These authors were inclined to believe that anemia of the vasomotor center resulting from arteriolosclerosis is the cause of some cases of hypertension. Evans examined the arterioles of the brain microscopically in thirty-five cases of primary hypertension. In twenty-one instances they were normal, and in the remaining fourteen cases, only a few arterioles in the pia mater showed sclerosis. Kahler explains some cases of primary hypertension on the basis of sclerosis of the arteries of the brain.

Sclerosis of varying degree in the arteries of the base of the brain is found in a great many cases of primary hypertension; but it is also found frequently in nonhypertensive cases. There is no convincing anatomic evidence that it is an underlying cause of hypertension, but it is of course responsible for many of the symptoms of the disease.

Anrep and Starling devised an ingeniuos experiment by which the head, neck and right arm of an animal are supplied with blood from a heart-lung preparation, while the rest of its body is supplied by its own heart. An increase of pressure in the thoracic aorta is followed by a reflex general vasodilatation with a fall of blood pressure. An increase of blood pressure in the brain is followed immediately by a direct vasodilatation of the vessels of the rest of the body with a fall of blood pressure, while a decrease of blood pressure in the brain has the opposite effect. This reaction occurs whether the vagi are cut or intact.

This experiment is generally considered to support the hypothesis that anemia of the brain (from arterial or arteriolar disease) is the basis of primary hypertension.

3. *Emotional and Sensory Disturbances.*—It is a matter of common clinical experience that excitement of any kind tends to raise the blood pressure even of normal persons. A single moderately high reading does not mean true hypertension unless the subject is quiet and entirely free from anxiety of any kind. Severe pain, such as lead colic or the gastric crises of tabes, may cause acute hypertension. Some persons react unusually in this way to emotions and painful sensations; we are accustomed to speak of their condition as "nervous temperament," "vasomotor instability," etc. One may infer that in such persons the vasomotor center is hyperirritable and that it reacts excessively to stimuli of psychic or peripheral origin. Von Monakow believes that unusual nervous instability may be the basis for the development of a true permanent hypertension. O'Hare and Walker are apparently of the same opinion. They report that in 42 per cent of their cases, they

obtained an early history of vasomotor instability, such as nervousness, epistaxis, menorrhagia, migraine and cold and sweaty cyanotic hands. These phenomena, however, are the early symptoms of the disease itself. A person with a well defined example of "vasomotor instability" commonly has hypertension. It is by no means proved that persons of "nervous temperament" develop permanent hypertension oftener than those of "phlegmatic type."

That the stimuli from the environment have some effect on blood pressure is also shown by the effects of rest and sleep. Rest in bed causes a definite temporary fall of blood pressure in the great majority of cases of primary hypertension, a fact which should be borne in mind in appraising the value of therapeutic procedures. However, when the patient resumes his occupation, the blood pressure commonly returns to its former level. During sleep, the systolic blood pressure of normal persons usually falls from 20 to 25 mm. of mercury. In hypertension, the pressure may fall from 30 to 60 mm. of mercury (Müller). The diastolic pressure decreases slightly. In hypertension that progresses to uremia, a fall of pressure does not occur (Katsch and Pansdorf). The blood pressure returns to its previous level as soon as the person awakens.

Emotional stress is an important factor in the aggravation of hypertension, but whether it actually causes the disease is another problem. It is conceivable that the vasomotor system of some persons is so unstable that all the trivial irritations of life act as irritants until a condition of permanently increased tonus is established; but at present there is no satisfactory evidence that this actually occurs.

4. *Hyperirritability of the Sympathetic Nervous System.*—Kylin considers this the basic condition in primary hypertension. In Raynaud's disease, there is a spastic contraction of the arteries of the lower extremity, which is relieved by lumbar sympathetic ganglionectomy (Adson and Brown). As the anatomic basis of this disease is not known, it may be considered due to overactivity or hyperirritability of the lumbar sympathetic system, or of other parts of the sympathetic system in cases in which the upper extremities or other parts of the body are involved.

A few cases of paroxysmal hypertension have been reported which were apparently due to malignant tumors. In Villaret's case of mediastinal lymphosarcoma the right vagus nerve was infiltrated, and irritation of this nerve was regarded by the author as the cause of the paroxysms. Mayo's patient had a large tumor near one suprarenal but not connected with it. The tumor was not considered of suprarenal origin. The paroxysms of hypertension disappeared after removal of the tumor. Irritation of the sympathetic system was considered a possible explanation of the hypertension.

On the whole, there are few facts to support the view that primary hypertension is a disease of the sympathetic nervous system.

5. *Increased Secretion of Epinephrine.*—After the discovery of the pressor effects of epinephrine, overactivity of the suprarenal glands was suggested by many investigators as the cause of primary hypertension. Subcutaneous or intravenous injection of extracts of the medulla is followed immediately by a sharp rise of blood pressure, which lasts a few minutes. Chronic hypertension does not result from repeated injections. In Addison's disease, in which the suprarenals are destroyed, there is a characteristic low blood pressure.

The theory of hypersuprarenalinemia is further supported by the fact that certain suprarenal tumors cause chronic hypertension. Labbé reported a paraganglioma of the suprarenal associated with paroxysmal hypertension. Oppenheimer and Fishberg compiled from the literature reports of several cases of suprarenal tumor accompanied by hypertension and reported two of their own. The reports include cases of cortical as well as of medullary tumor. Munk reports a case of medullary tumor with hypertension. Dieterle's patient, a child, aged 4 years, had generalized arteriosclerosis. For the most part, these cases of suprarenal tumor with hypertension occur in children or in young persons and have little clinical resemblance to primary hypertension. In our 420 cases, there were only three suprarenal tumors, and these were small cortical adenomas of a type that we have seen more frequently in the absence of hypertension. The theory of hypersuprarenalinemia likewise is not supported by biochemical investigations. The group of suprarenal tumors may be accepted as a definite form of secondary hypertension, but there is no proper support for the view that primary hypertension is due to overactivity of the suprarenals.

6. *Hyperthyroidism.*—In hyperthyroidism, the blood pressure is usually within normal limits, but in some cases a moderate hypertension is present at times during the course of the disease. Some confusion results from the fact that persons with primary hypertension sometimes develop hyperthyroidism also. The increased systolic pressure in this disease is interpreted by some authors as the result of increased minute volume of the heart; by others, as the result of vasomotor instability. The diastolic pressure is seldom increased.

There are occasional reports of cases of hyperthyroidism in which chronic congestive heart failure develops—such as is seen so frequently in cases of primary hypertension. The cases of this type that have come to our attention at necropsy, however, have been instances of hyperthyroidism associated with primary hypertension. Hyperthyroidism seems to be of little or no importance in the etiology of primary hypertension.

7. *Diabetes Mellitus.*—A great many writers have commented on the frequency of arteriosclerosis and hypertension in elderly persons with diabetes. Our necropsy records show that nineteen of seventy diabetic persons of all ages and seventeen of forty (42.5 per cent) over 50 years old had hypertension. Mr. R. F. Peterson collected from the literature 2,486 cases of diabetes in persons of all ages in which the blood pressure was given, and of this group, there was a systolic blood pressure of 150 mm. of mercury or more in 556 cases (22.3 per cent). Taking from the literature reports in which age groups are given, Peterson found that 236 of 583 (40.4 per cent) diabetic persons over 50 years old had hypertension (Rosenbloom, Kahn, Joslin, Maranon). It was pointed out in table 2 that hypertension occurs in approximately 15 per cent of the general population over 50 years of age, so that it is about 2.7 times as frequent in diabetic as in non-diabetic persons in advanced life. It is, however, relatively uncommon in persons with diabetes under 40 years of age.

Arteriosclerosis apparently bears about the same relation to diabetes as hypertension does, but no good statistical study is available since the clinical and pathologic criteria of arteriosclerosis are less exact than those of hypertension. The high incidence of gangrene in persons with diabetes points to the frequency of severe sclerosis of the arteries of the lower extremities.

The close relationship between diabetes, arteriosclerosis and hypertension is widely accepted, but its significance is not understood. One may accept the theory that arteriosclerosis causes atrophy of the pancreas which results in diabetes. But there is more evidence for the opposite view, namely, that diabetes intensifies and hastens the development of arteriosclerosis which results in hypertension when the arterioles become involved. In favor of the latter view is the frequent occurrence of diabetes in young persons without arteriosclerosis or hypertension. How can these cases be accounted for by the theory that diabetes is a result of arteriosclerosis? There is the further evidence that arteriosclerosis is more pronounced in cases of long duration than in those of unusual severity. It is also significant that 40 per cent of diabetic persons over 50 years old have hypertension; but only 5.5 per cent of hypertensive persons over 50 years old have diabetes. Diabetes, therefore, appears to be at least a contributory cause in some cases of arteriosclerosis and hypertension. This relationship offers a clue to the problem of arteriosclerosis. It has been suggested that the hypercholesterolemia of diabetes is the condition that accentuates arteriosclerosis.

8. *Disease of the Kidneys.*—No other organ shows such an intimate relation to hypertension as the kidney. The degree as well as the frequency of hypertension varies with the different forms of renal disease. These will be considered separately.

Glomerulonephritis: In this disease, hypertension is practically constant, though it is much more pronounced in subacute and chronic types than in the acute form. In the latter, the elevation of blood pressure is often slight and may be overlooked if the patient is first seen after recovery has set in. In chronic forms of long duration the blood pressure is maintained at a high level, and a definite cardiac hypertrophy develops.

Congenital Cystic Kidney: Fahr saw six cases of this disease, four with and two without hypertension. Details were not given. Volhard says that hypertension may occur even in the absence of renal insufficiency. Veil reported three cases in women 42 to 56 years of age with hypertension but without cardiac hypertrophy. Rosenberg and Munter published three case reports: the first case was that of a woman, aged 51; blood pressure decreased from 150 systolic and 100 diastolic to 133 systolic and 95 diastolic, and to 123 systolic and 75 diastolic; death resulted from uremia; the heart weighed 250 Gm. The second case was that of a woman, aged 48; the blood pressure was 135 systolic and 75 diastolic; death resulted from uremia; the heart was a little large but recurrent endocarditis was present. The third case was complicated by a true nephritis.

In our postmortem records the following reports of eight cases of congenital cystic kidneys in adults occur: (1) a woman, aged 33; postoperative death; blood pressure not read; heart, 350 Gm.; kidneys, 1,150 Gm.; (2) a woman, aged 44; uremia; blood pressure not read; heart, not enlarged; kidneys, about 1,200 Gm.; (3) a man, aged 52; fracture of skull; blood pressure not read; heart, 480 Gm.; kidneys, 1,290 Gm.; (4) a woman, aged 42; uremia; blood pressure not read; heart, not enlarged; kidneys, 3,330 Gm.; (5) a woman, aged 61; lobar pneumonia; blood pressure, 124 systolic and 73 diastolic; heart, 300 Gm.; kidneys, 750 Gm.; (6) a woman, aged 45; uremia; blood pressure (terminal) 90 systolic and 50 diastolic; heart, 292 Gm.; kidneys, 1,505 Gm.; (7) a man, aged 59; uremia; blood pressure 124 systolic and 82 diastolic; heart, 250 Gm.; kidneys, enormously enlarged; (8) a woman, aged 27; uremia and acute endocarditis; blood pressure (terminal), 78 systolic and 52 diastolic; heart, 240 Gm.; kidneys, 1,680 Gm.

The blood pressure was normal in the four cases in which it was read, and cardiac hypertrophy was present in only one instance. The available information is therefore strongly against the view that congenital cystic disease of the kidneys is accompanied by persistent hypertension.

Nephroses: The nephrosis which accompanies the toxemia of pregnancy is regularly accompanied by hypertension. The kidneys are

greatly enlarged and cloudy, but there is no renal insufficiency. Death is not due to the renal lesion. The hypertension in this disease may not be of renal origin.

The other forms of nephrosis are seldom associated with hypertension. Janeway and Volhard have both noted acute hypertension in nephrosis caused by mercuric chloride. It seems to occur in the early stages of anuria. Fahr records a case of hypertension and cardiac hypertrophy with advanced amyloid disease of the kidneys. Hypertension of sufficient intensity and duration to cause cardiac hypertrophy is apparently rarely found in pure nephrosis.

Hydronephrosis and Urinary Obstruction: Von Monakow reports a rise of blood pressure to 170 mm. of mercury caused by a ureteral stone. The pressure fell to 112 mm. of mercury after the stone was removed. Volhard lists urinary obstruction as one of the causes of hypertension. Brasch gives the details of three cases of urinary obstruction due to infiltrating carcinoma of the uterus. The blood pressure would rise to high levels (in one instance 210 systolic and 160 diastolic) during the periods of anuria, but would drop to normal shortly after relief from the obstruction. A great many reports deal with the acute hypertension that follows obstruction from prostatic hypertrophy and the fall of blood pressure that follows immediately on relief from the obstruction. Full records a drop from 230 to 145 mm. of mercury in fifteen minutes, and another from 210 to 140 mm. of mercury within a few minutes after catheterization.

In cases of long standing hydronephrosis, the blood pressure may be moderately elevated. In the case of elderly men with prostatic hypertrophy and hydronephrosis, one must not ascribe the hypertension to hydronephrosis without careful study, since a true primary hypertension often occurs at this time of life. It has not been proved that a definite cardiac hypertrophy can be caused by urinary obstruction alone.

Pyelonephritis: We have not seen any instances of cardiac hypertrophy or hypertension in this disease, nor have we found any detailed reports of such a case in the literature. Volhard, however, states that such cases occur.

Primary Contracted Kidneys: The contracted kidneys resulting from arteriolosclerosis are associated with unusually high blood pressure.

Experimental Renal Lesions: (1) An appreciable rise in blood pressure does not result from the removal of both kidneys or ligature of both renal arteries. (2) Pässler and Heinike report that surgical removal of a large part of the kidney tissue was followed by cardiac hypertrophy, but Anderson could not confirm their results. In his series of carefully controlled experiments, approximately 65 per cent of the renal tissue was removed, and the animals were kept in a state

of renal insufficiency for a long time, but hypertension did not develop. (3) Hartmann produced marked roentgen-ray atrophy of both kidneys in dogs. The animals developed definite hypertension as well as uremia. (4) Pedersen produced severe chronic passive congestion of one kidney in rabbits by constricting the renal vein and enclosing the kidney in a capsule to prevent the development of collateral circulation. The kidney undergoes a slow progressive atrophy. Definite hypertension develops and persists until the kidney has become small.

Renal Hypertension: It appears that acute hypertension may result from urinary obstruction during the period of anuria in sublimate nephrosis and in the toxemia of pregnancy, but none of these conditions seem to give rise to a persistent hypertension, since there is no cardiac hypertrophy. Aside from the primary contracted kidney, the only persistent hypertension of renal origin is associated with glomerulonephritis.

Several theories have been proposed to account for the relationship between renal disease and hypertension. Two of these will be discussed.

(a) Retention of a toxic substance in the blood. This theory does not account for the acute hypertension of urinary obstruction, since the pressure falls within a few minutes after the obstruction is relieved. Renal insufficiency resulting from the removal of both kidneys or a large part of the renal tissue does not cause hypertension. In chronic glomerulonephritis, the blood pressure is high a long time before any known substances are retained in the blood. Uremia resulting from pyelonephritis or congenital cystic kidney is seldom accompanied by hypertension. No one has succeeded in demonstrating pressor substances in the blood in any form of renal insufficiency. The substances that are known to be retained in renal insufficiency (urea, creatinine, chlorides) do not cause hypertension. If some unknown substance causes the rise of blood pressure, it must be assumed that it is held back by certain kinds of diseased kidneys and not by others.

(*b*) Reflex irritation of the vasomotor center or the sympathetic ganglions resulting in generalized increased tonus of arterioles. Theoretically, this idea is consistent with our present knowledge of the phenomenon. Obstruction in the kidney alone cannot cause hypertension, since the vascular area involved is too small. One must assume that the renal lesion in some way causes generalized increase of arteriolar tonus. The simplest interpretation of this is a reflex, although this has not been proved. If one assumes tentatively that a reflex occurs, the basis of the reflex must still be explained. Why does it occur in some forms of renal disease and not in others? The anatomic types of renal disease that are regularly accompanied by hypertension are glomerulonephritis and arteriolosclerosis, in which there is always narrowing and closure either of glomerular capillaries or arterioles or

of both structures. Narrowing of the arterioles and capillaries causes increased resistance to the blood flow, and therefore the secreting cells of the kidneys will receive less blood in a unit of time if the blood pressure remains constant. But if the organism reacts by increasing the blood pressure, the unit volume of blood for the secreting renal cells may be maintained. In congenitally cystic kidneys and in advanced pyelonephritis there is extensive disuse atrophy of vessels leading to atrophic areas of parenchyma, but there is no actual narrowing of small vessels, as in the forms discussed, and therefore no increased resistance to blood flow. This theory is consistent with Hartmann's experimental hypertension in which there is obviously narrowing of the small renal vessels. It is also in harmony with Pedersen's experimental hypertension, in which there is unquestionably obstruction in the renal circulation. This view explains hypertension of renal origin as a compensatory process. It is recognized that the reflex nature of the process has not been proved.

9. *The Menopause.*—There is a widespread opinion among physicians that a relatively benign form of hypertension frequently occurs in women at the menopause. It is said to follow the artificial (operation, roentgen ray) as well as the natural climacteric (Meier, Munk). Some authors believe that it is due to the cessation of ovarian function, and they point to the beneficial effects of ovarian therapy in support of their opinion. Munk believes that in some cases the hypertension becomes permanent.

Schlesinger reports a careful study of eighty-five patients in the climacteric and comes to the following conclusions: The climacteric often causes marked instability of the blood pressure, but not an increase. It does not cause permanent hypertension. The fluctuations of blood pressure are more marked after artificial than after natural menopause, and also more prominent after sudden than after gradual cessation of the menses. Those who have just passed the menopause show greater fluctuations than those who passed it some time ago.

Kisch, in a study of thirty-nine cases in which the climacteric was brought on by operation, finds nineteen patients with a continuously normal blood pressure. Sixteen showed wide variations in the systolic pressure; in a typical case it varied from 125 to 170 mm. of mercury. Three had chronic nephritis. Only one showed continuous hypertension that was not explained. Kisch also studied the blood pressure of 253 women between the ages of 42 and 52 years. Of these, 138 never had a pressure above 140 mm. of mercury. Sixty-one had a pressure above 140 continuously, but in fifty-eight the increase was attributed to some associated disease. Fifty-four women showed marked instability of the blood pressure, which is easily confused with true permanent hyperten-

sion. Instability of blood pressure was found in 21 per cent of women between the ages of 42 years and 52 years and in 40 per cent of women after artificial menopause. Kisch does not consider the menopause a cause of true permanent hypertension.

Lehfeldt took daily blood pressure readings in fifty-six cases of natural and of artificial climacteric. The diastolic pressure varied only a little. Seven patients had a systolic blood pressure above 140 mm. of mercury. Ten of those with pressure below 140 and three with pressure above this level showed fluctuations of more than 15 mm. of mercury. Half of those with instability showed some associated disease. Lehfeldt believes that neither increase nor instability of the blood pressure is characteristic of the climacteric.

Our observations show that so far as the onset of symptoms is concerned, there is no relation to the menopause. Hypertension as a cause of death is somewhat more frequent in men than in women between the ages of 40 years and 60 years. Our statistics would, of course, not include cases of hypertension that end in recovery.

The most thorough reports in the literature indicate that such hypertension as does occur as a result of climacteric disturbances is transitory or intermittent and does not develop into primary hypertension. One expects to find primary hypertension in from 10 to 12 per cent of women from 40 to 60 years old.

10. *Inheritance.*—A great many observers who have written articles on primary hypertension have been impressed with the importance of heredity and have given a few illustrations from their own experience; but there have been few systematic studies directed toward this particular problem. Weitz studied the family history in eighty-two cases of hypertension. Sixty-three (76.8 per cent) patients said that one (fifty-four) or both (nine) parents died of heart disease, dropsy or stroke. In 267 controls who did not complain of any symptoms referable to hypertension (blood pressure not read), only 30.3 per cent gave a similar heredity. The parents of the patients in the group with hypertension died at a much earlier average age than those of the controls. The parents of young persons with hypertension died at an earlier age than those of old persons with hypertension. Thirty-eight brothers or sisters of patients with hypertension over 55 years old were examined; eighteen of these had a systolic pressure above 150 mm. of mercury. Weitz says that in his opinion hypertension is a dominant character in heredity.

O'Hare, Walker and Vickers mention several families each with several cases of hypertension. In 300 cases of hypertension, 68 per cent gave a family history of apoplexy, heart disease, nephritis, arterioscle-

rosis or diabetes in one or more members. One hundred and twenty-eight controls over 45 years old gave such a family history in only 37.5 per cent.

Rosenbloom gives the history of one family in which both parents died of cerebral hemorrhage at the age of 45 years. Two of their daughters, aged 33 years and 35 years, did not have hypertension. The eight other children, all over 40 years old, developed hypertension, and four were dead at the time of the report. In agreement with the view that hypertension is a constitutional factor are the reports that it is rare among the Chinese (Cadbury).

The available evidence indicates strongly that hypertension is hereditary and familial, but much more extensive studies are needed. The published reports deal with only two generations, which is hardly adequate for the solution of a problem in inheritance. A little more certainty in the diagnosis of the disease in the parents is desirable, since not all cases of heart disease, nephritis and diabetes are instances of hypertension.

If inheritance is accepted as a fact, there still remains the question as to what is inherited. Is a subnormal arterial system or an unstable vasomotor system inherited?

11. *Obesity.*—The majority of observers find an increased incidence of hypertension with obesity. In seventy hospitalized cases of obesity, Aubertin finds the systolic pressures to be as follows: five above 250 mm. of mercury; thirty, from 200 to 250; twenty-one, from 170 to 200; nine from 150 to 170, and five below 150. In twenty-four ambulatory cases with the same degree of obesity, however, fifteen patients had a systolic pressure at or below 150 mm. of mercury; five, from 150 to 200, and four, above 200.

Terry finds that of sixty-three obese women (average weight 202 pounds) thirty-seven had hypertension (average pressure 173 systolic and 96 diastolic). He believes that the majority of obese women who seek medical advice have hypertension.

Rose finds that the blood pressure of obese persons could be reduced notably by diets that reduce body weight.

Many obese persons, however, do not have hypertension, and the disease frequently occurs in those who are underweight.

12. *Infection.*—The view was once widely prevalent among clinicians that hypertension is caused or at least aggravated by focal infections. Such physicians therefore advised the removal of tonsils and suspected teeth and spent much time in searching for hidden foci. This view has now been largely abandoned but is still prevalent in some parts of this country. The idea is unsound in theory, since the known bacterial poisons have a depressor rather than a pressor action. It has also been

shown conclusively in practice that the removal of teeth or tonsils not obviously diseased is rarely of any benefit and often does harm. The same principles that govern the treatment for infection in general should be applied in cases of hypertension. There is no satisfactory evidence that an infection can cause a rise of blood pressure.

As regards the rôle of cholesterol and high protein diet, little of a positive nature has been determined, and, since we can add nothing of importance, these topics will not be discussed.

COMMENT

True primary or essential hypertension must be sharply distinguished from secondary or symptomatic forms. The diagnosis of primary hypertension should not be made clinically unless there is or has been a persistent elevation of blood pressure of unknown cause or hypertrophy of the heart of left ventricular type without evidence of the diseases that cause this form of hypertrophy. The transitory forms (excitement, pain, menopause, etc.) are easily distinguished by continuous observation of the patient. The hypertension that accompanies the toxemia of pregnancy may be difficult to distinguish from the primary form, if there has been no study of the patient prior to the onset of her illness. Pregnancy commonly causes a marked aggravation of symptoms in primary hypertension. In the differential diagnosis one should remember: 1. The toxemia of pregnancy does not cause cardiac hypertrophy. 2. Sclerosis of the retinal arteries indicates primary hypertension. 3. In the simple toxemia of pregnancy, the blood pressure returns to normal within one month after the uterus is emptied. 4. Uncomplicated toxemia of pregnancy seldom causes renal insufficiency.

Hypertension from urinary obstruction seldom is difficult to diagnose. It is usually easy to demonstrate obstruction or a lesion of the spinal cord. Hypertension is usually only moderate and does not cause hypertrophy of the heart or cardiac failure.

The clinical differentiation between primary hypertension and chronic glomerulonephritis may present difficulties, and cases of the latter disease of many years' duration may be clinically indistinguishable from primary hypertension of the renal type. The following differential points are of value: Chronic glomerulonephritis shows typically only moderate cardiac hypertrophy and hypertension. Secondary anemia is always present in the advanced stages. There may be dyspnea and edema, but there is no cyanosis or passive congestion of the liver. Death is nearly always due to renal insufficiency. Sclerosis of the retinal arteries is seen only in cases of many years' duration. Apoplexy and coronary disease seldom occur in glomerulonephritis. The majority of patients are under 40 years of age.

Persons with primary hypertension commonly have a larger heart and a higher blood pressure than those with glomerulonephritis. Secondary anemia is seldom seen, except when there is renal insufficiency. Signs of cardiac failure are often noted. Apoplexy and coronary disease are frequent complications. Sclerosis of the retinal arteries can usually be observed. Only about 10 per cent of these patients die of uremia; 90 per cent are over 40 years of age.

The distinction between hypertension with slowly developing uremia and chronic glomerulonephritis of many years' duration cannot always be made clinically, since the symptoms, including changes in the eyegrounds, may be practically the same.

It is probable that a systolic pressure of 145 mm. of mercury represents a definite hypertension. We have used 150 mm. of mercury as the line of division in order to be more sure of including only true hypertension. Life insurance records indicate that pressures below 150 in persons without symptoms do not shorten life. However, we have the record of one patient whose pressure remained around 145 for about one year and then rose to a much higher level (180), where it remained until his death.

Cardiac hypertrophy of the left ventricular type, all known causes of hypertrophy being excluded, is the best anatomic evidence of primary hypertension; but the hearts of many patients with hypertension are only slightly enlarged. The size of the heart is believed to depend on the duration of the disease, the constancy of the high pressure and the nutritive condition of the cardiac muscle.

All cases of chronic congestive heart failure without valvular disease or pericardial adhesions apparently belong to the hypertensive group. None of these hearts weighed less than 400 Gm., but objection may be made against the inclusion of cases in which the blood pressure was normal. We believe that these persons had high blood pressure at some previous time, since the records in many of our cases show a fall of blood pressure from cardiac failure several months before death and since the majority of the patients had renal arteriolosclerosis. But possibly there is a form of idiopathic hypertrophy that is never accompanied by hypertension.

Coronary sclerosis must have some causal relation to hypertension, since the association is too frequent to be accidental. Coronary disease causes malnutrition and weakening of the myocardium, which tends to lower the blood pressure, so that we cannot believe that it causes hypertension. It is consistent with our present knowledge, however, to believe that coronary sclerosis is a senile change, like arteriosclerosis elsewhere, which develops independently of hypertension and which may run its course even to a fatal termination without it, but when hypertension is associated, the increased strain accelerates and intensifies

the arterial disease and makes it more prominent anatomically and clinically than it is in cases in which hypertension is not present.

The same explanation may be offered for the close relation between hypertension and cerebral hemorrhage and thrombosis, i. e., the increased strain on the vessels from high blood pressure accelerates the natural course of arteriosclerosis and favors early rupture or occlusion.

The problem of the relation of hypertension to renal arteriolosclerosis has interested pathologists for many years. The fundamental facts are not yet agreed on, because few authors explain exactly what they mean by "arteriole." If the afferent glomerular vessels only are meant, then arteriolosclerosis is not found in some cases of undoubted hypertension, but if vessels larger than these are called arterioles, arteriolosclerosis is found in nearly all cases of hypertension and in many elderly persons who do not have hypertension.

Another source of confusion arises from the fact that each author makes his own definition of hypertension. Some have considered a systolic pressure above 140 mm. of mercury as hypertension, while others consider only those above 180. Similarly, a heart weight of 400 Gm. has been considered by a few authors as sufficient evidence of hypertension, while others would require a weight of 450 or 500 Gm.

These discrepancies make it difficult to compare the observations of different authors as regards the frequency of renal arteriolosclerosis in hypertension.

The different interpretations of the frequent association of renal arteriolosclerosis and hypertension will be given briefly:

1. Renal arteriolosclerosis causes hypertension. In support of this hypothesis, it is argued that (*a*) arteriolosclerosis is always present in hypertension or (*b*) that it is present in all but a small percentage of cases, which are to be interpreted as extrarenal in origin. (*c*) The point is also urged by Fahr that if hypertension causes arteriolosclerosis, it should do so in the skin, muscles and other organs as well as in the kidneys. According to this view, the basis of hypertension is obstruction in the renal circulation, which gives rise to reflex general vasoconstriction and hypertension.

2. Hypertension causes renal arteriolosclerosis. The arguments for this hypothesis are: (*a*) Typical cases of hypertension occur without renal arteriolosclerosis. (*b*) Arteriolosclerosis is found in chronic glomerulonephritis, especially in cases of long duration (Fishberg). Sometimes it is so pronounced that even a microscopic distinction from primary hypertension is not easy. It does not develop to any considerable extent until there has been a long period of high blood pressure. (*c*) Whatever explanation one adopts for arteriolosclerosis (hypertension, toxins, inheritance), it is just as difficult to explain why the

kidney is affected so much more frequently and intensely. One must assume hypersusceptibility of the renal arterioles in any case. (*d*) There is evidence that increased intravascular pressure favors arterial degeneration. There is much more arterial disease in the lower extremity, where the hydrostatic pressure is added to the blood pressure, than in the upper extremity. Extremities paralyzed from childhood are said not to develop arteriosclerosis. There is a marked increase of elastic tissue in the renal arteries in long standing cases of hypertension. In aortic stenosis, the arch of the aorta is commonly free from sclerosis, even in advanced life.

On the whole, the evidence seems to favor the hypothesis that hypertension causes renal arteriolosclerosis. Arteriolosclerosis is not a distinct pathologic entity but an extension of arterial disease into terminal branches. It might readily result from increased intravascular tension. Aside from the renal group in which there is definite obstruction in the renal circulation, there is no relation between the size of the heart or the height of the blood pressure and the degree of sclerosis of the renal arterioles. This discrepancy, of course, is an argument against both hypotheses. According to the second theory, however, it might be explained as a variation in resistance of arterioles to strain; but according to the first theory, one must explain how slight sclerosis or no sclerosis causes as much hypertension and cardiac hypertrophy as severe sclerosis.

The theory that hypertension is due to arteriosclerosis or arteriolosclerosis of the medulla with resulting anemia of the vasomotor center has some adherents. It is supported by the convincing experiments of Cushing and of Anrep and Starling. This hypothesis can neither be denied nor affirmed until extensive studies have been made of the blood vessels of the medulla in persons with hypertension and in those with a normal blood pressure. It would seem that narrowing of the basilar artery and it branches would be more effective in causing anemia than narrowing of arterioles. Sclerosis of occasional arterioles is not sufficient proof of anemia of the vasomotor center. If the basis of hypertension is really anemia of the brain, one would expect to see clinical signs of cerebral anemia (dizziness, fainting, etc.) when the blood pressure is lowered by venesection or rest in bed. As far as our observations go, this rarely occurs.

We do not have any theory of the etiology of primary hypertension to propose. In the light of the meager available knowledge of the disease, it seems that study should be directed toward disturbances of vasomotor mechanisms. Primary hypertension does not appear to be caused by vascular disease, but it puts an additional strain on the arterial system which accelerates and intensifies arterial degeneration. In this way we may explain its close association with arteriolosclerosis,

coronary sclerosis and sclerosis of the small arteries of the brain. It is, however, probable that when a severe arteriolosclerosis of the kidney has developed, the circulatory obstruction tends to raise the blood pressure to higher levels.

SUMMARY

Primary hypertension is defined as (*a*) a persistent systolic pressure of 150 mm. of mercury or higher of unknown origin, or (*b*) cardiac hypertrophy of left ventricular type (450 Gm. or more, female; 500 Gm. or more, male) not associated with any disease known to cause hypertrophy. Definite sclerosis of the afferent glomerular arterioles is almost conclusive evidence of hypertension.

On the basis of the clinical course and the manner of death, the 420 cases are arranged in five groups: myocardial insufficiency, 187; coronary sclerosis, 67; encephalic group (hemorrhage and thrombosis), 81; renal insufficiency, 36; miscellaneous (accident and intercurrent disease), 49.

Ninety and six-tenths per cent of the patients were over 40 years of age and 74.3 per cent were over 50 years of age at the time of death.

In the entire group, the corrected ratio of males to females is 1.4:1; in the coronary and miscellaneous groups, 2.7:1 and 2.8:1, respectively.

About 15 per cent of deaths in persons over 50 years old are due to primary hypertension.

All cases of chronic congestive heart failure of idiopathic type probably belong in the hypertensive group. The blood pressure may fall to the normal level several months before death.

Coronary sclerosis is much more frequent and intense in hypertensive than in nonhypertensive cases. There is satisfactory evidence that approximately two thirds of all clinical cases of coronary disease are associated with hypertension.

There is satisfactory evidence that approximately 85 per cent of the cases of apoplexy of the foregoing types are associated with hypertension.

Approximately half of the kidneys of the entire group appeared entirely normal on macroscopic examination. About one fourth showed a definite fine pitting of the external surfaces but no atrophy. Only about 15 per cent showed sufficient atrophy to be called "primary contracted kidney," and only 8.5 per cent of the patients died of uremia. There are all degrees of atrophy of the kidneys in hypertension.

Of thirty-six cases of hypertension with renal insufficiency (malignant hypertension, Fahr) one was a case of acute hypertension ending in acute uremia, eight were cases of chronic hypertension ending in acute uremia, and twenty-seven were cases of chronic hypertension in which uremia developed slowly.

In the nine cases in which uremia developed rapidly, necrosis of the afferent glomerular arterioles was a frequent microscopic condition, and occasional glomeruli showed inflammatory changes.

The renal arteries within the parenchyma of the kidney showed sclerosis (hyperplastic-elastic intimal thickening) of varying degree in 97.6 per cent of the cases. These vessels are usually sclerosed, but to a less extent in elderly patients without hypertension. Only marked hyperplastic-elastic intimal thickening of the renal arteries indicates hypertension.

The afferent glomerular arterioles showed sclerosis varying from slight to severe degree in 89.4 per cent of all cases of hypertension. There is less renal arteriolosclerosis in the coronary and the miscellaneous groups than in the others. Not all observers use "arteriole" in the same sense.

Definite sclerosis of the afferent glomerular arterioles is rarely if ever seen except in association with hypertension.

Ten and six-tenths per cent of the patients in our series did not show sclerosis of the afferent glomerular arterioles.

There is probably no fundamental difference between arteriosclerosis and arteriolosclerosis.

Certain forms of arteriosclerosis (coronary disease, sclerosis of small arteries of the brain) are closely related to hypertension, while sclerosis of the aorta and peripheral arteries did not show any definite relation to hypertension.

Hypertension may be produced experimentally by increased intracranial pressure. In man, this situation seems to occur only in the case of intracranial hemorrhages that spread diffusely over the surface of the brain.

Hypertension may be caused by renal diseases, especially those characterized by obstruction to the circulation (e. g., chronic glomerulonephritis), but primary hypertension is apparently not produced in this manner except possibly in cases of acute uremia.

Hypertension is two or three times as frequent in elderly persons with diabetes as in nondiabetic persons of the same age group, but only about 5.5 per cent of persons with hypertension develop diabetes.

BIBLIOGRAPHY

Adson and Brown: Raynaud's Disease, Ann. Clin. Med. **5**:161 and 168, 1926.

Allbut, C.: Diseases of the Arteries, New York, The Macmillan Company, vol. 1, 1915, p. 345.

Alvarez, W. C.: The Surprising Frequency of Hypertension in a Group of Young Drafted Men, California State J. Med. **17**:367, 1919; Blood Pressures in 15,000 University Freshmen, Arch. Int. Med. **32**:17 (July) 1923.

Anderson, H. C.: Experimental Renal Insufficiency, Arch. Int. Med. **37**:297 (March) 1926.

Anrep and Starling: Central and Reflex Regulation of the Circulation, Proc. Roy. Soc. London **97**:463, 1924-1925.

Aubertin, C.: Obésité et hypertension, Bull. Soc. méd. de hôp. de Paris **1**:977, 1922.

Bell, E. T.: Outlines of Pathology, University of Minn. Publications, 1924. The Distinction Between Chronic Glomerulonephritis and Hyperpiesia, Minnesota Med. **9**:1, 1926.

Bell and Hartzell: Studies on Hypertension: The Relation of Age to the Size of the Heart, J. M. Research **44**:473, 1924.

Billings, F.: Am. Heart J. **2**:689, 1927 (discussion).

Bordley and Baker: A Consideration of Arteriosclerosis of the Cerebral Vessels and the Pathogenesis of Hypertension, Bull. Johns Hopkins Hosp. **38**:320, 1926.

Bordley and Baker: A Consideration of Arteriosclerosis of the Cerebral Vessels and the Pathogenesis of Hypertension, Bull. Johns Hopkins Hosp. **39**:229, 1926.

Brasch, W.: Ueber die klinischen Erscheinungen bei langdauerender Anurie, Deutsches Arch. f. klin. Med. **103**:488, 1911.

Brooks, H.: A Preliminary Study of Visceral Arteriosclerosis, Am. J. M. Sc. **131**:778, 1906.

Burton-Opitz and Edwards: Ueber die durch Hirndruck verursachte Steigerung des Blutdruckes, Wien. med. Wchnschr. **66**:505, 1916.

Cadbury, W. W.: The Blood Pressure of Normal Cantonese Students, Arch. Int. Med. **30**:362 (Sept.) 1922.

Campbell and Blankenhorn: The Effect of Sleep on Normal and High Blood Pressure, Am. Heart J. **1**:151, 1925-1926.

Cushing, H.: Concerning a Definite Regulatory Mechanism of the Vasomotor Center Which Controls the Blood Pressure During Cerebral Compression, Bull. Johns Hopkins Hosp. **12**:290, 1901.

Diehl and Sutherland: Systolic Blood Pressure in Young Men, Arch. Int. Med. **36**:151 (Aug.) 1925.

Dieterle, R. R.: Malignant Hypernephroma Coincident with Arteriosclerosis in Children, J. Nerv. & Ment. Dis. **65**:42, 1927.

Evans, G.: A Contribution to the Study of Arteriosclerosis, Quart. J. Med. **55**:215, 1921.

Faber: Die Arterisklerose, Jena, 1912.

Fahr: Ueber Nephrosklerose, Virchows Arch. f. path. Anat. **226**:119, 1919; Zur path.-anat. Unterscheidung der Schrumpfnieren nebst Bemerkungen zur Arteriosklerose der kleinen Organarterien, Frank. Ztschr. f. Path. **9**:15, 1912; Kurzer Beitrag zur Frage der Hypertonie, Berl. klin. Wchnschr. **58**: 730, 1921; Ueber die Beziehungen von Arteriolensklerose, Hypertonie und Herzhypertrophie, Virchows Arch. f. path. Anat. **239**:41, 1922.

Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650 (May) 1925.

Fisher, J. W.: Report of Blood Pressure Committe, Proc. Assn. Life Insur. Med. Dir. Am. **9**:59, 1922-1923; The Diagnostic Value of the Sphygmomanometer in Examinations for Life Insurance, J. A. M. A. **63**:1752 (Nov. 14) 1914.

Frost, H. M.: Hypertension and Longevity, Boston M. & S. J. **193**:241, 1925.

Fleischmann, P.: Der hohe Blutdruck, Deutsche. med. Wchnschr. **51**:2059 and 2104, 1925.

Friedemann, U.: Ueber die Veränderungen der kleinen Arterien bei Nieren-Erkrankungen, Virchows Arch. f. path. Anat. **159**:541, 1900.

Full, H.: Blutdruck und Harnabflussbehinderung, Berl. klin. Wchnschr. **57**:1149, 1920.

Gaskell, J. F.: On the Changes in the Glomeruli and Arteries in Inflammatory and Arteriosclerotic Kidney Disease, J. Path. & Bact. **16**:287, 1911-1912.

Gull and Sutton: Chronic Bright's Disease with Contracted Kidney (Arterio-capillary Fibrosis), Medic. Chir. Tr. **55**:273, 1872.

Harpuder, K.: Arteriosklerose, Schrumpfniere und Blutdruck, Deutsches Arch. f. klin. Med. **129**:74, 1919.

Hartmann, Bolliger and Doub: Experimental Nephritis Produced by Irradiation, Am. J. M. Sc. **172**:487, 1926.

Herxheimer: Ueber das Verhalten der kleinen Gefaesse der Miiz, Berl. klin. Wchnschr. **54**:82, 1917.

Herxheimer: Niere und Hypertonie, Verhandl. d. deutsch. path. Gesellsch. **15**:211, 1912.

Hueck, W.: Anatomisches zur Frage nach Wesen und Ursachen der Arteriosklerose, München. med. Wchnschr. **67**:535, 573 and 600, 1920.

Hunter, A. W., quoted from Frost.

Jaffe, R. H.: The Vascular Changes of the Kidney in Hypertension, Am. J. M. Sc. **169**:88, 1925.

Janeway, T. C.: Important Contributions to Clinical Medicine During the Past 30 Years From the Study of Human Blood Pressure, Bull. Johns Hopkins Hosp. **26**:341, 1915.

Jores, L.: Wesen und Entwickelung der Arteriosklerose, Bonn, 1903; Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, Virchows Arch. f. path. Anat. **178**:367, 1904; Ueber den pathologischen Umbau von Organen, Virchows Arch. f. path. Anat. **221**:14, 1916.

Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923, p. 579.

Kahler, H.: Die Blutdrucksteigerung, ihre Entstehung und ihr Mechanismus, Ergeb. d. inn. Med. u. Kinderh. **25**:265, 1924; Die verschieden Formen von Blutdrucksteigerung, Wien. klin. Wchnschr. **36**:265, 1923.

Kahn, M.: Angina Pectoris of Diabetes, J. A. M. A. **76**:570 (Feb. 26) 1921.

Katsch and Pansdorf: Die Schlafbewegung des Blutdrucks, München. med. Wchnschr. **69**:1715, 1922.

Kaufmann, F.: Klinisch-experimentelle Untersuchungen zum Krankheitsbilde der arteriellen Hypertension, Ztschr. f. klin. Med. **100**:677, 1924.

Kieth, N. H.: Classification of Hypertension and Clinical Differentiation of the Malignant Type, Am. Heart. J. **2**:597, 1927.

Kisch, F.: Untersuchungen über Hypertonien im Klimakterium, München. med. Wchnschr. **69**:1082, 1922.

Kylin, E.: Zur Frage über die Aetiologie der essentiellen Hypertoniekrankheit, Klin. Wchnschr. **4**:806, 1925.

Labbé, Tinel and Doumer: Crises solaires et hypertension paroxystique en rapport avec une tumeur surrenale, Bull. et mém. Soc. méd. d. hôp. de Paris **1**:982, 1922.

Lehfeldt, H.: Klimakterium und Blutdruck, Zentralbl. f. Gynäk. **50**:2889, 1926.

Lippmann, A.: Apoplexie, Enzephalomalazie und Blutdruck, Deutsche. med. Wchnschr. **44**:907, 1918.

Löhlein, M.: Ueber Schrumpfnieren, Beitr. z. allg. Path. u. path. Anat. **63**: 570, 1917; Zur Pathogenese der vasculären Schrumpfnieren, Med. Klin. **12**:741, 872 and 1042, 1916; Zur Nephrocirrhosis arteriosclerotica, Med. Klin. **14**:136, 1918.

MacWilliam, J. A.: Blood Pressures in Man Under Normal and Pathological Conditions, Physiol. Rev. **5**:303, 1925.

Maranon, G.: Ueber Hypertonie und Zuckerkrankheit, Zentralbl. f. inn. Med. **43**:169, 1922.

Mayo, C. H.: Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve, J. A. M. A. **89**:1047 (Sept. 24) 1927.

Meier, F.: Ueber die klimarkterische Blutdrucksteigerung, Med. Klin. **16**:704, 1920.

Minor: Am. Heart J. **2**:690, 1927 (discussion).

Von Monakow, P.: Blutdrucksteigerung und Niere, Deutsches Arch. f. klin. Med. **133**:129, 1920.

Mönckeberg, J. G.: Ueber die reine Mediaverkalkung der Extremitätenarterien und ihre Verhalten zur Arteriosklerose, Virchows Arch. f. path. Anat. **171**:141, 1903.

Müller, C.: Vasomotorische Veränderungen bei chronischen Herzinsufficienz, Deutsches Arch. f. klin. Med. **151-152**:47, 1923.

Munk, F.: Ueber Arteriosklerose, Arteriolosklerose und genuine Hypertonie, Ergeb. d. inn. Med. u. Kinderh. **22**:1, 1922; Ueber die genuine insbesondere die klimakterische Hypertonie, Ztschr. f. Geburtsh. u. Gynäk. **90**:403, 1926; Die Hypertonie als Krankheitsbegriff, Berl. klin. Wchnschr. **56**:1205, 1919; Zur klin. Diagnose der Schrumpfniere, Med. Klin. **12**:1341 and 1360, 1916.

O'Hare and Walker: Arteriosclerosis and Hypertension, Arch. Int. Med. **33**:343 (March) 1924.

O'Hare, Walker and Vickers: Heredity and Hypertension, J. A. M. A. **83**: 27 (July 5) 1924.

Oppenheim, F.: Ueber den histologischen Bau der Arterien in der wachsenden und alternden Niere, Frankfurt. Ztschr. f. Path. **21**:57, 1918.

Oppenheimer and Fishberg: The Association of Hypertension with Adrenal Tumors, Arch. Int. Med. **34**:631 (Nov.) 1924.

Pal, J.: Ueber permanente Hypertonie, Med. Klin. **5**:1312, 1909; Arteriosklerose und Arteriolosklerose, Wien. klin. Wchnschr. **35**:647, 1922.

Pässier and Heinike: Versuche zur Pathologie des Morbus Brightii, Verhandl. deutsch. path. Gesellsch. **9**:99, 1905.

Pedersen, A. H.: A Method of Producing Experimental Chronic Hypertension in the Rabbit, Arch. Path. **3**:912 (May) 1927.

Riebold, G.: Deuernde erhebliche Blutdrucksteigerung als Frühsymptom einer Gehirnarteriosklerose, München. med. Wchnschr. **64**:1390, 1917.

Rose, R. H.: Weight Reduction and its Remarkable Effect on High Blood Pressure, New York M. J. **5**:752, 1922.

Rosenberg and Munter: Zur Frage der renalen oder extrarenalen Blutdrucksteigerung, Deutsche med. Wchnschr. **50**:1437, 1924.

Rosenbloom, J.: Familial Hypertension, J. Lab. & Clin. Med. **8**:681, 1923; Blood Pressure Studies in 140 Cases of Diabetes, J. Lab. & Clin. Med. **7**:392, 1922.

Sawada, K.: Blutdruckmessungen bei Arteriosklerose, Deutsche. med. Wchnschr. **30**:425, 1904.

Schlesinger, O.: Zur Frage der klimakterischen Blutdrucksteigerung, Berl. klin. Wchnschr. **58**:545, 1921.

Symonds, B.: The Blood Pressure of Healthy Men and Women, Proc. Assn. Life Insur. Med. Dir. Am. **9**:22, 1922-1923.

Terry, A. H.: Obesity and Hypertension, J. A. M. A. **81**:1283 (Oct. 13) 1923.

Villaret, Bloch, Bariéty and Lappas: Crises hypertensives paroxystiques au cours d'un lymphosarcome du mediastin superieur, Presse méd., no. 54, 1926. p. 856.

Volhard, F.: Ueber Wandlungen in der Nephritislehre, Wien. med. Wchnschr. **72**:429, 1922; Die doppelseitigen hämatogen Nierenerkrankungen, in Möhr and Stöhlein: Handbuch der inneren medizin, vol. 3, p. 1149-1722.

Volhard and Fahr: Die Brightische Nierenkrankheit, 1914.

Wallgren, A.: Die Arterien der Niere und der Blutdruck, Acta med. Scandinav. **56**:356, 1922.

Watanabe, S.: Ueber die Arteriosklerose der Hautgefässe, Schweiz. med. Wchnschr. **51**:780, 1921.

Weitz, W.: Zur Aetiologie der genuinen oder vasculären Hypertension, Ztschr. f. klin. Med. **96**:151, 1923.

Ziegler, E.: Ueber die Ursachen der Nierenschrumpfung, Deutsches Arch. f. klin. Med. **25**:586, 1880.

DEATH FROM BRONCHIAL ASTHMA

REPORT OF THREE CASES *

W. B. KOUNTZ, M.D.
AND
H. L. ALEXANDER, M.D.
ST. LOUIS

Death from bronchial asthma is a rare occurrence. This clinical observation has been established for more than 100 years. In all, about thirty cases in which autopsies with microscopic studies were made have been reported in the literature.[1] Several of the cases obviously were not true bronchial asthma, and in other cases death took place from intercurrent disease. Rackemann [2] reviewed the twenty-one cases collected by Hüber and Koessler,[3] and added one other. From these he deduced that no more than eleven patients died from the immediate effects of asthma.

The study of three cases of bronchial asthma with detailed postmortem analysis, is therefore, of importance, particularly because each of these deaths may be attributed directly to the effects of asthma. Moreover, some postmortem observations hitherto undescribed are reported.

REPORT OF CASES

CASE 1.—*History.*—P. T. K., aged 52, a clerk, entered Barnes Hospital Feb. 1, 1926, complaining of asthma. There was no family history of allergic disturbances. The only significant events in the history were frequent attacks of hives during the past twenty years, and an evident allergic rhinitis for the last three years.

The present illness began in June, 1924, with sudden, severe shortness of breath. The patient had had a cold in the head and it is noteworthy that the dyspnea appeared shortly after he took "Rinex" for the first time. The dyspnea was characterized by wheezing, and a smothering sensation. It subsided completely within a few hours following the injection of epinephrine hydrochloride. A second similar attack occurred a few weeks later, without evident cause. Thereafter, paroxysms increased in frequency and severity until they occurred several times a day. This continued until death. There was an associated cough, with the production of purulent tenacious sputum. During the last year of illness the general health was impaired with the loss of appetite, weakness and loss of weight.

---

* From the Departments of Pathology and Internal Medicine, Washington University School of Medicine and Barnes Hospital.

1. Grimm, V.: Das Asthma, Jena, Gustav Fischer, 1925, p. 68.

2. Rackemann, F. M.: Boston M. & S. J. **194**:531, 1926.

3. Huber, H. L., and Koessler, K. K.: Pathology of Asthma, Arch. Int. Med. **30**:689 (Dec.) 1922.

Examination and Course.—On physical examination, the significant observations were as follows: Weight, 60 Kg.; undernourishment; moderate emphysema with partial fixation of the chest. Resonance was impaired over both apexes, particularly the left, in which many subcrepitant râles were heard after coughing. During paroxysmal attacks typical asthmatic breathing was heard, also numerous moist râles and rhonchi. The heart and abdomen were normal.

The positive laboratory observations showed a blood eosinophilia with a maximum of 13 per cent. Spirals, eosinophils and Charcot-Leyden crystals were seen in the sputum. Intradermal tests were positive to horse dander, timothy and ragweed pollens and pyrethrum.

The patient remained in the hospital for five months, during which time his attacks increased in frequency and severity until they became almost continuous. There was an occasional period of mild irregular fever. On July 17, the patient had a severe attack and sent for an intern. Extreme dyspnea and a gray cyanosis of the face were present. The heart sounds were not audible because of noisy breathing; the pulse rate was faint, rapid and irregular in force but not in rhythm. Within a few minutes the pulse stopped and the patient lost consciousness. Ineffectual respiratory effort persisted for about one minute. Epinephrine hydrochloride injected into the heart did not cause any appreciable response.

Although this patient was 51 years of age at the onset of the asthma, the coincident history of an apparent allergic rhinitis, the characteristic asthmatic paroxysms, the positive allergic skin reactions, the eosinophilia in the blood and sputum and Charcot-Leyden crystals in the sputum established the diagnosis of bronchial asthma. There were, however, signs of a complicating pulmonary tuberculosis at the left apex.

Postmortem Examination.—Lungs: As the chest plate was removed, the pleura was found to be adherent to it. When the adhesions were cut, the lungs collapsed. The heart and lungs were in the normal position. The heart did not seem to be enlarged. The pleural cavity was completely obliterated with fibrous structures. There was, at the apex of the left lung, a cavity which measured 3.5 cm. in diameter, into the base of which a 2 mm. bronchus opened. Many small tubercles were present in the area about the cavity. The right lung was similarly involved with a tuberculous process, but to a lesser extent. The area involved about one eighth of the upper lobe of the left organ and about one sixteenth of the upper lobe of the right organ. Under the microscope, a moderate degree of emphysema was present in places, while in others the alveoli were collapsed and the walls thickened. In some of the emphysematous areas the fibrous tissue in the alveolar walls was atrophic, and small vacuolated spaces were seen in it. In other places the walls were broken and several sacs opened together, resulting in emphysematous cavities. These cavities appeared to be the result of absorption and the breaking of the degenerated tissue. The cell outlines in the atrophic area were lost. The tissue took a pink stain resembling the basement membrane in the bronchi and appeared to be a hyaline degeneration of the lung tissue. The change just described involved only a portion of both lungs near the hilum in all lobes. The remainder of the lung tissue showed areas of moderate emphysema alternating with areas in which partial atelectasis was seen. Thus, some bronchi were surrounded by emphysematous areas, whereas about others the air spaces appeared to be collapsed.

Bronchi: In the gross sections of the lungs the small bronchi were widely dilated, and they could not be distinguished from small blood vessels. Under the microscope, the bronchioli up to 3 mm. were widely dilated, the epithelium was

flat and the walls were thin. The alveoli immediately around them were collapsed and appeared to have been pressed on by the dilated bronchi and thus caused to collapse. A few of the 2 to 3 mm. bronchi contained within their lumina a small amount of whitish, thick, mucoid exudate. Microscopically, this consisted of pale, pink-staining, streaky material in which there were chiefly lymphocytes and desquamated epithelial cells, but an occasional eosinophil and plasma cell was seen also. The walls of these smaller organs showed some lymphocytic infiltration.

In the 3 to 4 mm. bronchi, the basement membrane becomes prominent and the muscle layer more distinct than normal. Although these layers were not increased in thickness, the basement membrane took a clear hyaline stain, and the muscle was compact. There was an increase in the lymphocytes present in the wall with an occasional eosinophil and plasma cell. The exudate in the lumen was somewhat increased in amount and consisted of approximately the same characteristics as those described in the smaller bronchi. The blood vessels in the bronchial walls were somewhat dilated. Gross sections of 4 to 5 mm. bronchi were seen to contain considerable whitish exudate in their lumen. They were dilated and the wall was thicker than normal. Under the microscope, each lumen was seen to contain a considerable amount of the pink-staining exudate in which there were about equal numbers of lymphocytes and eosinophils, many desquamated epithelial cells and also a few plasma cells. The epithelium was thickened, and from three to four rows of nuclei were present at its base. The basement membrane was dense and stood out as a clear hyaline band completely encircling the bronchus, and it extended back under the epithelium of the ducts and glands. The subepithelial layer was much thicker and more prominent in structures of this size than in the smaller bronchi. It was infiltrated with eosinophils and lymphocytes in about equal numbers. The muscle layer was distinct, and an occasional small group of leukocytes was present within it. The bronchial glands were of approximately normal size and the alveoli contained a mucoid substance. There was considerable lymphocytic infiltration about portions of the glands. The outer coat of the bronchi showed irregular accumulations of lymphocytes in the walls with an occasional eosinophil.

Gross sections of 5 to 6 mm. bronchi were definitely thickened, and the lumina of many were filled with thick, mucoid, whitish exudate. They did not appear to be dilated. Microscopically, the exudate consisted of the same material as that described in the 4 to 5 mm. bronchi. Eosinophils were seen in groups and scattered singly throughout the exudate. In some of the bronchi many small pink-staining crystals were seen, and about many of them eosinophils were grouped. Many desquamated epithelial cells undergoing a mucoid degeneration were present.

The epithelium was hypertrophic, and many goblet cells were present on its surface. In some areas it was desquamated and could be seen in the lumen. The basement membrane had the same appearance as that of the 4 to 5 mm. tubes. It was thicker, however, and occasionally broken, and its ends were separated. At these points, accumulations of eosinophils could be seen, and it appeared as if they were passing from the subepithelial layer into the lumen.

The subepithelial layer was thick and infiltrated with leukocytes, chiefly eosinophils with some plasma cells and lymphocytes. The muscle layer was thickened, and dense. It completely embraced the bronchi, and the tissue encircled was thrown into folds. The glands were relatively large and contained foci of round cells, some eosinophils and a few plasma cells. The cellular infiltration was most marked in the periphery of the gland, but in places could be seen extending

toward its center along the septum. At the periphery of the glands the acini were large and well preserved, while at the center of the glands many of the cells had undergone a mucoid degeneration, and the alveoli were filled with mucus. Some of the fibrous tissue between the glands had disappeared, and communications between the ducts were present. The predominating cell in this area was the lymphocyte, but in some areas an equal number of eosinophils was present with them.

In gross sections of 6 to 7 mm. bronchi, the walls were thickened as in the preceding group, and the pale pink muscle layer extended around them. The lumina of many were filled with exudate. Microscopically, the same picture was seen as was noted in 5 to 6 mm. structures, only in this group the muscle layer was much thicker. The exudate nearly completely filled the lumen, and many eosinophils and Charcot-Leyden crystals were present in it. The muscle layer was thickened, and in some sections it was dense. In other sections large masses of leukocytes extended into it from the surrounding tissue, and areas of muscle had disappeared and been replaced by them. The cartilage in some of the sections was larger than normal and had large vacuoles within its substance. The capsule was thickened, and about some portions there was a lymphocytic infiltration.

In the 7 to 8 mm. bronchi the lumina were only partially filled with exudate which had the same appearance as that described previously. In gross sections the walls were thickened but the muscle coat did not stand out distinctly as in the preceding group.

Microscopically, the epithelium was somewhat hypertrophic, but fewer goblet cells were present within it. The basement membrane had the clear hyaline appearance as previously noted, but it was not as thick as that in the 6 to 7 mm. group. The subepithelial layer in some sections was thickened, but in others it was essentially normal. Some eosinophilic infiltration was present, but not as much as was seen in the 6 to 7 mm. group. The muscle layer was less distinct and also not as thick; it was less cellular, and small spaces could be seen between the fibers. The glands and ducts were filled with mucus containing an occasional lymphocyte.

Heart: The pericardium was smooth and shiny throughout. Section of the heart showed a slightly granular appearance of the myocardium and white streaks extending through it. None of the chambers were dilated or hypertrophied. The measurements of the chamber walls were as follows: right auricle, 0.2 cm.; left auricle, 0.3 cm.; right ventricle, 0.55 cm., and left ventricle, 1.5 cm. The endocardium was smooth and shiny. There was no thickening of any of the valve leaflets. Only a slight degree of sclerosis of the aorta and coronary vessels was present. The valvular circumferences were: tricuspid, 11 cm.; mitral, 11.5 cm.; pulmonary, 7 cm., and aortic, 7 cm.

Microscopic examination of the heart showed a slight thickening of the pericardium in places. The thickening consisted of a loose fibrous tissue in which few lymphocytes were present. The myocardium was normal except for an occasional muscle fiber containing light-staining areas, and some slight increase in fibrous tissue about the vessels. Sudan III stain did not show any fat in the muscle fibers. The measurements of the nuclei of the fibers averaged 4 by 5 microns which is normal.

Case 2.—*History.*—G. D., aged 60, with no occupation, entered Barnes Hospital Dec. 15, 1924, with the chief complaint of asthma. He was admitted five subsequent times with the same complaint. The family history did not show any evidence of allergic manifestations. Of sole significance in the history was the occurrence of hay-fever in the spring for several successive seasons about thirty

years before. The present illness dated back to the summer of 1899 when the patient, while at work with a threshing machine, had a sudden severe respiratory difficulty which lasted for several hours. A similar attack occurred six months later, and thereafter about every six to twelve months until the spring of 1924. These attacks were sudden in onset, with a sensation of smothering, and they were paroxysmal in character. The intervals between attacks always were free from symptoms until the spring of 1924, when suddenly the attacks increased in frequency and severity and soon averaged four a day. Epinephrine hydrochloride always relieved the attacks, and this drug was used constantly from that time on. Between the paroxysms, cough and wheezing developed. During the year previous to his examination there had been a dependent edema.

Examination and Course.—Physical examination during the last year of illness revealed the following pathologic observations. There was cyanosis of the face and extremities. The chest was quite fixed and there was apparently a diffuse emphysema. During the paroxysms, signs typical of bronchial asthma appeared, and at all times a few rhonchi and moist râles were audible. The cardiovascular systems did not show any abnormality other than a low blood pressure (98 systolic and 75 diastolic), although considerable edema was present in both ankles and feet.

Of significance in the laboratory evidence were a blood eosinophilia to a maximum of 15 per cent, and eosinophils, spirals and occasionally Charcot-Leyden crystals in the sputum. A positive intradermal reaction to ragweed pollen extract was obtained. Another etiologic factor was discovered, namely, phenol and certain coal tar products which contain the phenol ring. One drop of phenol in a tumblerful of water induced a most violent attack. It is noteworthy that measurements of the heart diameters in a 6 foot film did not show enlargement and that electrocardiographic tracings were normal. The venous pressure, however, was increased. Between paroxysms this averaged 7.5 cm. of water, and during an attack it rose to 13.5 cm. The vital capacity measured 1,700 cc., which was 43.8 per cent of the patient's estimated normal capacity.

With the exception of about four months during the summer, the patient was under continuous observation in the hospital from November, 1925, to November, 1926, the date of his death.

The course in the hospital was marked by continuous asthma, which was diminished during the following events; during an attack of bronchopneumonia, during the intravenous administration of typhoid vaccine, and, for a short period, during the induction of a hyperthermia by physiotherapeutic methods. The patient was observed in an attack during the night of Nov. 10, 1926. Three hours after, he was found dead in bed.

The history of paroxysmal attacks of dyspnea occurring first at the age of 35 and preceded by attacks of hay-fever, indicate that this case was one of allergic asthma. The blood and sputum eosinophilia, the presence of spirals and the positive intradermal test to pollen confirm this diagnosis. There was an evident complicating emphysema. The edema of the lower extremities was not associated with any evident cardiac lesion.

Postmortem Examination.—Lungs: The pleural cavities of both organs were obliterated by strong fibrous tissue adhesions to the chest wall. However, there were not any adhesions binding them to the mediastinal structure. On removal they were seen to be voluminous and to weigh together 1,900 Gm. At both apexes, emphysematous blebs were present, varying from 1 to 4 cm. in diameter. The degree of involvement of the two organs was equal, and the marked emphysema was limited to the apexes. A few small scars of old healed tuberculous lesions

were present on the median surface of both organs. Incision of the organs showed that the entreme emphysema was most pronounced just under the pleura. The remainder of the organs showed many small emphysematous cavities throughout, the substance varying from 0.5 to 1 mm. in diameter. The lungs collapsed as the air was forced out of them. Microscopically, a few red blood cells were present in the alveoli at the bases of the organs. In the same areas some pink, albuminous precipitate was seen.

Bronchi: The 0.5 to 3 mm. bronchi were widely dilated, and some contained fibrin and polymorphonuclear leukocytes in their lumina. Others contained a small amount of pink-staining exudate, which appeared to be mucoid in character. A few polymorphonuclear leukocytes, plasma cells, lymphocytes and eosinophils were seen in it. The epithelium was low and cuboidal in type. A basement membrane could not be seen. The subepithelial layer was not thickened, but an occasional polymorphonuclear leukocyte and plasma cell was present. The muscle layer, if present, was well developed, but not particularly prominent. Hyperemia was noted in the peribronchial tissues. About the 1 mm. bronchi there was some lymphocytic and plasma cell infiltration. About the 2 to 3 mm. bronchi large areas of lymphocytic infiltration were present. Groups of plasma cells were also seen.

Microscopically, the lumen of the 3 to 4 mm. tubes contained a small amount of exudate consisting of mucus in fine threads with leukocytes enmeshed within. The leukocytes consisted chiefly of polymorphonuclears in considerable abundance. A few lymphocytes, plasma cells and eosinophils were present. Much of the epithelium was desquamated, and only rows of nuclei appeared on the surface. The desquamated epithelium was seen in the lumen. The basement membrane came into prominence as a thin clear hyaline layer which varied in thickness from 0.002 to 0.004 mm. It was thrown into many folds and at some points rested directly on the muscle. The subepithelial layers showed some infiltration with polymorphonuclear leukocytes, lymphocytes and plasma cells. This area, however, was not thickened. In some areas, because of the folding of the basement membrane, it was thin. The muscle layer was prominent but not thickened. Many eosinophils were present between the muscle bundles. The cartilage was small, and its capsule was thickened and in some areas appeared to be undergoing a solution, as its edge had a granular appearance. The glands were small, and their epithelium was normal. There was some lymphocytic infiltration about the glands as well as in the peribronchial tissues.

The 4 to 5 mm. bronchi were not dilated, and a few contained a small amount of mucoid exudate within the lumen. Microscopically, the lumina of a few of the 4 to 5 mm. bronchi were contracted and smaller in proportion to the outside diameter. The majority of them, however, showed only a small degree of contraction. The lumen contained some pink-staining material in which were seen desquamated epithelial cells and leukocytes. The epithelium and basement membrane were thrown into folds. The outer portion of the epithelium was broken away and much of it was lined with one or two layers of nuclei. The basement membrane was somewhat thicker than those in the slides of the 3 to 4 mm. bronchi and could be seen extending down into ducts where it gradually thinned out and faded into a loose connective tissue. The subepithelial tissue was thickened and infiltrated with plasma cells in considerable abundance, and also by a few lymphocytes and eosinophils. The thickness of the subepithelial layer varied with the folds of the basement membrane. At the points at which the folds extended inward, the subepithelial tissue was thin. The muscle layer was prominent and dense. It did not, however, appear to be thickened. The glands were

small, and much of the epithelium was undergoing a mucoid degeneration, as the cell outline could not be made out. Considerable lymphocytic infiltration was present about them. The ducts were dilated and contained a pink, granular precipitate in the lumen. Some of the cartilage in the sections had a thickened capsule, and the cartilage itself was vacuolar.

In gross sections, the walls of the 5 to 6 mm. bronchi were seen to be definitely thickened, and the lumina of many contained a thick mucoid exudate which was easily broken. The amount varied with the location of the bronchus. Those in the lower lobes contained more than those in the upper ones. Under the microscope, each lumen contained a small amount of pink-staining hyaline material and a considerable number of polymorphonuclear leukocytes and plasma cells. The muscle layer was from two to three times normal thickness and it was dense. The fibers and nuclei were large. A slight degree of leukocytic infiltration was present in the muscle layer in this group of bronchi.

The walls of the 6 to 7 mm. bronchi were definitely thickened and the lumina were normal. The muscle layer in the unfixed state could be seen as a clear band in the bronchial wall. Considerable characteristic exudate was present in the lumen of these tubes. The epithelium and basement membranes presented the same characteristics as those seen in the 5 to 6 mm. bronchi. The subepithelial layer was thick, and a few small blood vessels were present in it. Just under the basement membrane, eosinophils and plasma cells lay in close proximity to one another. The basement membrane was well defined and attained its maximum thickness in this group. There was an occasional break in this membrane and eosinophils could be seen filling the space. The subepithelial layer was thickened and contained many eosinophils. External to this, however, the layer of leukocytes gave way to a granular, fibrous tissue in which only an occasional leukocyte was present. The muscle layer stood out prominently and was definitely thickened. The nuclei and fibers were one and a half times larger than normal. The ducts of the glands were dilated and contained an exudate similar to that observed in the bronchi. Some of the acini were large, and the epithelium was undergoing a mucoid degeneration. Some plasma cell and eosinophilic accumulations were present in the stroma between the alveoli. They were not seen in great numbers anywhere.

The 8 to 10 mm. bronchi were thicker than normal. The muscle, although visible, could not be made out as distinctly as in the 6 to 8 mm. group. The peribronchial tissue seemed to have taken the greatest part in the process of thickening.

Under the microscope, the 8 to 10 mm. bronchi showed little exudate in the lumen. The epithelium was rather high and consisted of columnar, ciliated cells. The basement membrane was present but thinner than that noted before. The muscle layer in the greater portion of the sections was of normal appearance, but in a few it was denser than normal. Many of the epithelial cells of the glands were undergoing a mucoid degeneration; the ducts were dilated and contained considerable mucus within the lumen. The glands were of about normal size. The trachea and large bronchi (primary bifurcation) were found to be normal on examination.

Heart: The pericardium was smooth and shiny, and no adhesions were present. The myocardium was dark brown. A few small white areas were seen about the vessels in the base of the septum. On removal from the body, the organ was found to weigh 325 Gm. In regard to thickness, its walls were in the upper limit of normal. The right ventricle measured 4.2 mm., and the left 1.4 cm. The organ was soft and flabby. The chambers were about normal size. The

endocardium was smooth, and none of the valves were thickened. The valve circumferences were: tricupsid, 10 cm.; mitral, 10.5 cm.; pulmonary, 7 cm., and aortic, 6.7 cm.

The muscle bundles were widely separated and in some areas a pink albuminous precipitate could be seen between them. In one area in which the muscle was widely separated, red blood cells had accumulated, in addition to the pink precipitate. Otherwise, the organ was normal. A sudan III stain was negative for fat.

Nasal mucosa: In gross sections, the nasal mucus membrane was thickened and of grayish appearance.

Microscopic study of the membrane showed the submucous tissue to be greatly thickened; the glands were prominent and undergoing mucoid degeneration. Under the epithelium, a clear, hyaline basement membrane was noted. The connective tissue in the submucosa was loose and edematous, with many large vacuolated spaces in it. Lymphocytes and eosinophils were present in the connective tissue just under the basement membrane. A few large mononuclear leukocytes were observed. In the region of the middle turbinals, the epithelium was markedly hyperplastic—in some areas as many as fifteen layers thick. The outer portion of the thickened epithelium consisted of cells which contained large vacuoles of mucus.

The epithelium lower down (about the left inferior turbinal) was not as hyperplastic as that above. The submucous tissues were thicker, and a greater leukocytic reaction was present in them. Here, grouped about the blood and lymph vessels, and also just under the basement membrane, were many lymphocytes and eosinophils. A marked amount of edema was present also. Several small areas were noted in the tissue in which leukocytes were accumulated and the tissue was undergoing necrosis and solution. The tissue, except for the edematous accumulation, had an appearance similar to that of the subepithelial layers of the bronchi.

Case 3.—*History.*—S. B., a farmer, aged 48, entered Barnes Hospital Feb. 27, 1928, with the chief complaint of asthma. There was no family history or past history of allergic disturbances. At the age of 19, the patient had had an abscess on one of the lungs which ruptured spontaneously without further symptoms. The present illness dated from childhood, when attacks of sudden shortness of breath first developed. These were of but a few hours' duration at that time. They had occurred every few months from that time until about two years before admission to the hospital, when there was a marked increase in the severity of the attacks, as well as in the frequency and duration. The attacks consisted of paroxysms of wheezing, chiefly nocturnal, followed by a cough, with the production of colorless, tenacious sputum which occasionally became blood streaked. No specific agent was known to cause attacks, and epinephrine hydrochloride relieved them promptly.

Examination and Course.—On physical examination, the essential observations included a moderate degree of cyanosis of the lips. The chest was markedly distended and fixed. Breathing apparently was entirely costal. Hyper-resonance and the auscultatory signs of marked emphysema were present. During paroxysms of dyspnea, sounds typical of bronchial asthma were heard. The borders of the heart were obscured by hyper-resonance, but nothing pathologic was elicited. The blood pressure was 115 systolic and 65 diastolic. The abdomen was normal except that the edge of the liver was palpable 5 cm. below the right costal margin in midclavicular line.

The laboratory observations showed a blood eosinophilia of 7 per cent. The sputum contained many eosinophils. A positive intradermal reaction to horse dander was elicited. The course in the hospital was marked by severe asthmatic paroxysms which occurred every few hours. Between attacks there was constant respiratory distress, and but little air seemed to enter the chest, owing, presumably, to extreme emphysema. Constant air hunger continued, and the patient gradually became more cyanotic and relapsed into semicoma. Finally, he became moribund, and a gray cyanosis appeared. Breathing was superficial in spite of marked respiratory effort. The pulse rate became weak and rapid, and death occurred without any evident pulmonary edema.

Evidently this case was one of bronchial asthma beginning in childhood and recurring frequently throughout life. As in cases 1 and 2, the attacks became almost constant for a year or two before death. The striking feature in this patient was the emphysema which apparently became so extreme that ventilation was no longer adequate to sustain life; and a respiratory death doubtless occurred, in the absence of pulmonary edema.

Postmortem Examination.—Lungs: The lungs together weighed 1,600 Gm. They were voluminous and did not collapse, but projected out of the chest when the breastplate was removed. The organs were pale white, and many emphysematous blebs were present on the surface. The pleura was smooth and thin, and adhesions were not present. The large bronchi contained considerable mucoid exudate.

Sections of the organs showed a marked degree of emphysema which was present throughout all lobes. At the apexes just under the pleura, large emphysematous cavities were observed, measuring from 3 to 4 mm. in diameter. Smaller cavities were present throughout both lungs.

Under the microscope, many of the alveolar walls were seen to be stretched thin, and some were broken. An occasional red blood cell was seen in the alveoli, and a few large mononuclear leukocytes containing bile pigment were present. The arterial walls were greatly thickened and in places appeared to be undergoing an endarteritis obliterans.

The small bronchi (1.5 to 3 mm.) in gross sections were widely dilated and could not be distinguished from blood vessels. The 3 mm. bronchi contained considerable exudate in the lumen.

Under the microscope, the bronchial walls were seen to be thin, and the lumina were widely dilated. A few lymphocytes and plasma cells were seen in the walls. The epithelium was made up of low, columnar cells. No basement membrane was seen, and the muscle layer was well developed but not excessively prominent. In the wall of the 2 to 3 mm. bronchi, areas of lymphocytic infiltration were noted in the peribronchial tissue. A few eosinophils were present in the subepithelial tissue and in the lumen.

In gross sections, the walls of the 3 to 6 mm. bronchi were seen to be thickened, and the lumina contained a thick mucoid material. Under the microscope, these bronchi were seen to contain a considerable amount of pink-staining, mucoid exudate in which there were many eosinophils and lymphocytes. The cells of the epithelium were the high, columnar type, many goblet cells being present. In areas the epithelium was completely torn away, and only one or two rows of nuclei were present on the basement membrane.

The basement membrane was prominent and varied in thickness. In the region of the ducts it was one and one half times as thick as elsewhere. At points there were breaks in it, and eosinophils could be seen passing into the lumen. Complete breaks had occurred in two bronchi, and the subepithelial

tissue was seen projecting into the lumina. It appeared as though pressure exerted by spasms of the muscle of the bronchi had caused a rupture of the basement membrane and protrusion of the subepithelial tissue. The bronchi were run in serial sections, and the lesion was found to be present for 6 mm. along the organs.

The 6 to 8 mm. bronchi showed a smaller amount of exudate in the lumen than the 4 to 5 mm. bronchi. The epithelium was rather high and consisted of columnar, ciliated cells. The basement membrane was present but somewhat thin, and small strands projected from it into the underlying tissues. The subepithelial layers were of about normal thickness, but a considerable number of eosinophils were present. The muscle layer was prominent, but not greatly thickened. The epithelium of the glands showed a similar mucoid change, as noted in other sections. The ducts of the glands were dilated and filled with the mucoid exudate. A few eosinophils had accumulated external to the muscle layer. Otherwise, the peribronchial tissue was relatively free from them.

Heart: The removal of the heart showed the pericardial surface to be smooth and shiny. The myocardium had a dark red granular appearance, and a few small white streaks were present in the substance. Otherwise, the myocardium was normal. The endocardium was smooth throughout. Both sides of the heart were dilated to some degree, chiefly, however, the right side. The right ventricle wall varied in thickness, as it measured 8 mm. at the upper portion, near the attachment to the auricle, and 4 mm. near the apex. The variation in thickness of the chamber wall was due to dilatation following a moderate hypertrophy. The left ventricle was also slightly dilated and moderately hypertrophied. The left ventricle measured 1.6 cm. in thickness. The respective valve circumferences were: tricuspid, 13 cm.; mitral, 11 cm.; pulmonary, 7.5 cm., and aortic, 7.1 cm. The organ weighed 400 Gm.

Microscopic examination showed a considerable increase in the fibrous tissue in the heart, chiefly about the blood vessels. In some areas the scars reached a maximum size of 0.5 cm. The blood vessel walls were thickened, and an occasional lymphocyte was present about them in the scar tissue. The stain for fat was negative.

DISCUSSION

Although there has been but little pathologic material from which to study the effects of bronchial asthma, certain definite lesions have been established. One of the most distinctive is the evident hypertrophy of the bronchial musculature at certain levels. This was demonstrated by Hüber and Koessler.[3] They distinguished the various layers of the bronchial wall, painstakingly measured the diameters of each, and then compared them with normal bronchi. The musculature of bronchi measuring from 3 to 7 mm. in outside diameter is much thicker than that of normal controls and comparatively thicker than that at other levels. This important observation supports the theory (which is still disputed) that an asthmatic paroxysm is due to muscle spasm, for the hypertrophied muscle implies increased function. The cases reported were studied in a like manner. They confirm the observations of Hüber and Koessler, in that not only the muscle layer (fig. 1) but the subepithelial layer also (lying between the epithelium and the muscle) is thickened at certain levels (fig. 2). The complete measure-

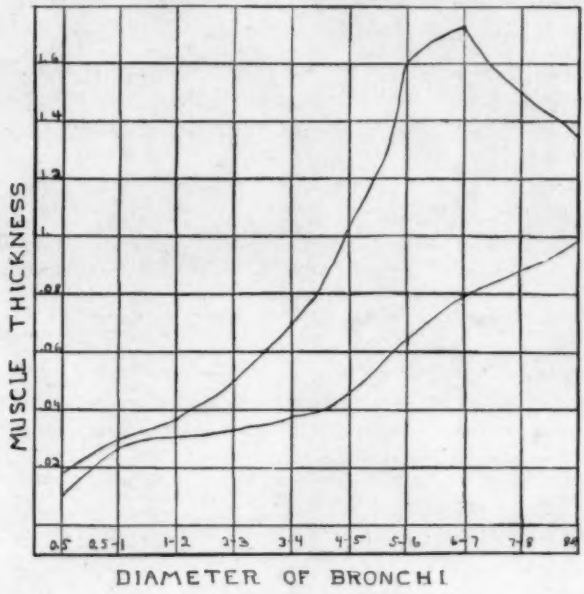


Fig. 1.—Thickness of muscle layer in relation to diameter of bronchi.

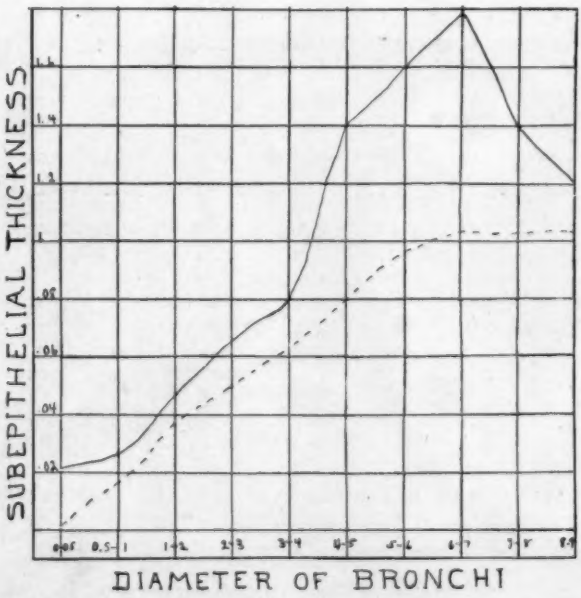


Fig. 2.—Thickness of subepithelial layer in relation to diameters of bronchi.

ments are given in the table; they may be compared with those in the article by Hüber and Koessler. Another indication of increased muscle spasm is the rupture of the basement membrane with extension of subepithelial substance into the bronchial lumen in one case. This was observed in two places, and has not been described heretofore (fig. 3).

Complete Measurements of Normal Bronchial Musculature and of That of Three Persons Who Died of Bronchial Asthma

Patient	Outside Diameter	Inside Diameter	Wall Thickness	Epithelial Thickness	Basement Membrane	Subepithelial Layer	Muscle Thickness	Gland Diameter
P. T. K.....	0.335	0.155	0.9	0.001	—	0.03	0.026	—
S. B.	0.43	0.29	0.07	—	—	0.018	0.022	—
G. D.	0.413	0.26	0.075	—	—	0.02	0.011	—
Normal	0.36	0.14	0.11	0.01	—	0.007	0.01	—
P. T. K.....	0.808	0.55	0.159	0.0031	—	0.0425	0.031	—
S. B.	0.74	0.54	0.1	—	—	0.016	0.036	—
G. D.	0.73	0.512	0.112	—	—	0.024	0.015	—
Normal	0.87	0.7	0.085	—	—	0.018	0.027	—
P. T. K.....	1.75	1.09	0.33	0.0085	—	0.040	0.037	—
S. B.	1.41	0.95	0.23	0.07	0.003	0.07	0.05	—
G. D.	1.36	0.763	0.297	—	0.0026	0.0276	0.023	—
Normal	1.7	1	0.35	0.023	—	0.039	0.03	—
P. T. K.....	2.29	1.6	0.34	0.0146	—	0.048	0.041	—
S. B.	2.2	1.2	0.5	0.01	0.007	0.09	0.1	—
G. D	2.28	1.26	0.517	—	0.0065	0.0309	0.027	—
Normal	2.7	1.7	0.5	0.033	—	0.05	0.032	—
P. T. K.....	3.6	1.75	0.95	0.026	—	0.05	0.055	—
S. B.	3.2	1.2	1.1	0.0409	0.017	0.13	0.14	0.35
G. D.	3.58	1.85	0.877	—	0.0026	0.0436	0.03	0.02
Normal	3.8	1.75	1.025	0.045	—	0.063	0.038	—
P. T. K.....	4.2	1.9	1.15	0.0267	—	0.18	0.06	0.27
S. B.	4	1.6	1.24	0.045	0.018	0.16	0.2	0.45
G. D.	4.2	2.06	1.07	0.0029	0.0111	0.0842	0.06	0.023
Normal	4.2	2.28	0.96	0.031	—	0.08	0.046	—
P. T. K.....	5.2	4.2	0.5	0.051	—	0.13	0.11	—
S. B.	5.2	2.9	1.16	0.054	0.012	0.25	0.22	0.65
G. D.	5.38	2.84	1.29	0.025	0.077	0.0945	0.164	—
Normal	5.1	3.2	0.95	0.056	—	0.095	0.064	—
P. T. K.....	6.33	3.17	1.58	0.054	0.009	0.162	0.124	1.
S. B.	6.4	2.2	2.1	0.057	0.03	0.17	0.18	0.07
G. D.	6.61	2.8	1.94	0.037	0.062	0.223	0.214	0.048
Normal	6.5	5	0.75	0.05	0.004	0.12	0.078	—
P. T. K.....	7.2	5.93	0.64	0.035	0.0032	0.121	0.19	1.2
S. B.	7.5	3.7	1.9	0.059	0.02	0.13	0.15	0.7
G. D.	7.1	3.9	1.63	0.048	0.032	0.18	0.11	0.053
Normal	7.6	5.5	1.0	0.042	0.006	0.12	0.087	0.032
P. T. K.....	8.5	5.3	1.6	0.052	0.011	0.12	0.17	0.9
S. B.	8.5	5.9	1.3	0.041	0.02	0.12	0.12	0.72
G. D.	8.2	4.6	1.8	0.024	0.025	0.12	0.11	0.047
Normal	8	5	1.5	—	—	0.09	0.1	—
P. T. K.....	9	5.4	1.8	0.1	0.012	0.14	0.13	0.6
S. B.	9.9	6.5	1.7	0.04	0.021	0.13	0.14	0.7
G. D.	9.79	5.17	2.31	0.01	0.028	0.13	0.12	0.12
Normal	9.5	5.5	2	—	0.0066	0.09	0.07	1.2

Another striking lesion which has been noted by various observers [4] was dilatation of the small bronchioles, below the levels of increased muscle thickness (fig. 4). This has been thought to be due to a pull on the bronchiole walls by the surrounding alveoli which were

4. Fashingbaur, H.: Wien. Arch. f. klin. Med. **4**:349, 1922. Schlecht, H.: Deutsches Arch. f. klin. Med. **98**:308, 1910.

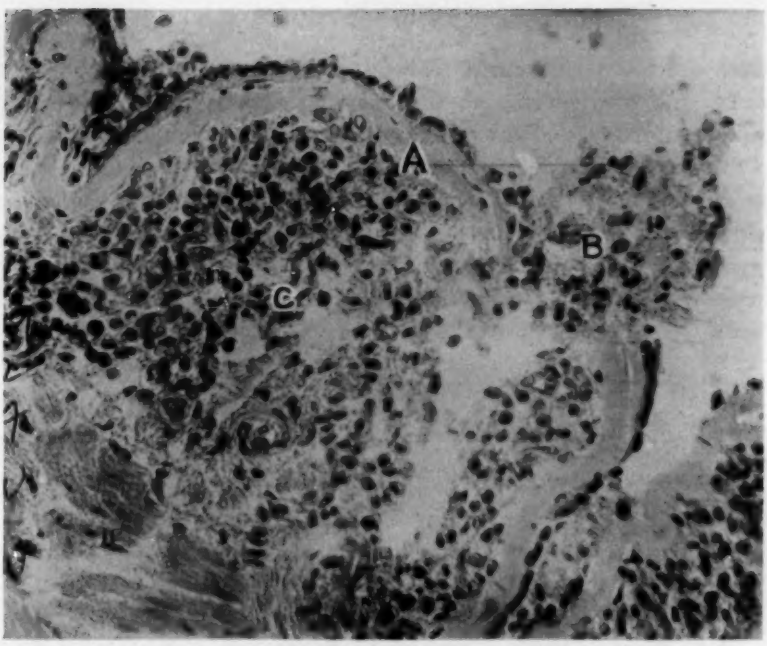


Fig. 3.—High power photomicrograph of wall of bronchus (5 mm.) showing basement membrane (*A*) and point of rupture; subepithelial tissue (*B*), and protrusion of subepithelial layer into lumen (*C*).

Fig. 4.—Small bronchus (1.5 mm.) showing dilatation and collapse of surrounding alveoli. A small amount of exudate is present in the lumen.

stretched from emphysema. This is not probable, for in sections from the foregoing cases the reverse was seen. The alveoli surrounding the bronchioles actually were collapsed from evident compression by the distended bronchioles. In all probability the bronchiolar dilatation was due to an increased air pressure within them which resulted from expiratory efforts to force air through the constricted bronchi which lay just proximal, at the level of increased muscle thickness (fig. 5) The intrabronchial pressure, therefore, is evidently great at all levels.

Fig. 5.—Large bronchus (5 mm.) showing contraction and folding of the wall, caused apparently by bronchial spasm.

and dilatation takes place except in the large tubes in which there is sufficient cartilaginous support to hold the tube rigid.

The presence of a tissue eosinophilia in the bronchial wall has been noted both in bronchial asthma [2] and in the lungs of guinea-pigs after anaphylactic shock.[5] Their presence in a given case of paroxysmal dyspnea is probably the most definite lesion diagnostic of bronchial

5. Schlecht, H., and Schwenker, G.: Arch. f. exper. Path. u. Pharmakol. **67**:137, 1912; ibid. **68**:163, 1912.

asthma. It is presumed from experimental evidence [6] that the eosinophils are attracted by foreign protein substances which have reached the lung. Their accumulation is greatest surrounding the muscle layer (fig. 6). In one striking section, these cells actually had invaded the muscle substance and caused its destruction. It would appear, thereby, that the foreign protein substance was attracted particularly to the bronchial musculature.

Other noteworthy observations were the great increase in size and numbers of the epithelial goblet cells, the thickened hyalinized basement membrane, which in places made large indentations in the bronchial

Fig 6.—Dilated ducts (*A*) and glands (*C*), containing a mucoid exudate in the lumen; basement membrane (*B*) prominent in ducts and glands.

wall and the dilated mucous glands and ducts (fig. 6). An interesting observation not described heretofore was a curious degeneration of the cartilage, appearing as large areas of absorption (fig. 7).

In case 3, a section from the nasal mucous membrane was studied, and its similarity to the epithelial and subepithelial layers of the bronchi was striking. This confirmed the clinical impression that the lesion of bronchial asthma involves both the upper and lower respiratory

6. Oeller, H.: München med. Wchnschr. **71**:218, 1924. Schilling, V.: Deutsche med Wchnschr. **51**:467, 1925.

tracts. No previous study of this tissue in bronchial asthma has been noted.

Until recently there has been a prevailing opinion that after prolonged bronchial asthma, organic changes occur in the heart, particularly hypertrophy of the right ventricle. Based on clinical evidence, some doubt has arisen concerning this belief,[7] and consequently the hearts were examined carefully. In case 3, in which extreme emphysema occurred, there was some dilatation and hypertrophy of the right ventricle, but this was not by any means marked. There is some doubt

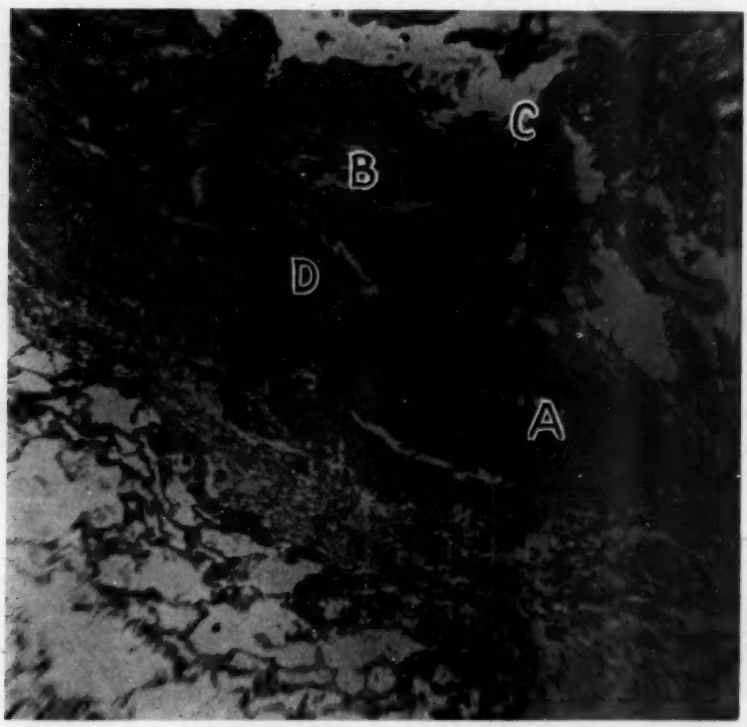


Fig. 7.—Section of bronchus showing: degeneration of cartilage (*A*) thickened muscle layer (*B*) and basement membrane (*C*). The fibrous tissue replacement of cartilage (*D*) should be noted.

whether this was the effect of bronchial asthma, as the left ventricle also showed hypertrophy which obviously could not be due to this. It is, therefore, possible that whatever caused the left-sided enlargement was responsible likewise for the right hypertrophy. In cases 1 and 2, dilatation and hypertrophy did not appear.

---

7. Alexander, H. L.; Luten, D., and Kountz, W. B.: Effect on Heart of Long-Standing Bronchial Asthma, J. A. M. A. **88**:882 (March 19) 1927.

In case 2, a dependent edema was constant for almost a year before death. This edema, with dyspnea on slight exertion, and cyanosis simulated heart disease. The essentially negative results of the examination of the heart both clinically and pathologically are, therefore, of interest. The dyspnea and cyanosis were evidently due to emphysema. The dependent edema may have been due to a retardation of venous flow, as evidenced by the high pressure in the veins observed in this case. Such a partial chronic venous stasis may induce subcutaneous edema, such as is seen in varicosed veins of the legs. Although the observations are as yet too limited to admit of positive statement, they indicate that the dependent edema, not infrequently seen in long-standing cases of bronchial asthma, need not be considered unequivocally a sign of cardiac failure.

CONCLUSIONS

1. Three cases in which the patients died of bronchial asthma have been reported with clinical and postmortem studies.

2. It was found that in the 3 to 6 mm. bronchi, there was thickening of the muscle and the subepithelial layers, a confirmation of the work reported by Hüber and Koessler. Likewise, a dilatation was observed in the small bronchi, a characteristic previously noted by Fashingbauer.

3. In addition, certain previously unreported evidence was found, such as a rupture of the basement membrane, infiltration and destruction of muscle by eosinophils, as well as destruction of the bronchial cartilage. An essential similarity between the lesions in the nasal mucous membrane and those of the epithelial and subepithelial layers of the bronchi was also discovered.

4. In two cases of asthma, one of twenty-five years' duration and the other of three years' duration, there was not any demonstrable disease in the heart. In one of the patients persistent edema of the legs was observed. From both a clinical and pathologic standpoint, the dependent edema must be considered to have an origin other than in the heart.

THE RELATIONS BETWEEN KUPFFER CELLS AND LIVER CELLS

FUNCTIONAL STUDIES *

R. H. JAFFÉ, M.D.
AND
S. L. BERMAN, M.D.
CHICAGO

To test the functional activity of the reticulo-endothelial system two methods have been recommended. Both make use of its storage capacity for foreign substances. Adler and Reimann [1] and Wilensky [2] injected congo red intravenously and determined its disappearance from the blood with the aid of a colorimeter. Only a dye which is taken up by the reticulo-endothelial cells is suitable for a test of their function. Adler and Reimann, Schellong [3] and Wilensky briefly mentioned the presence of dye granules in the histocytes of animals that have received injections of congo red. Smetana [4] and others said that congo red is not a vital stain.

In order to decide the question, from 5 to 10 cc. of a 1 per cent solution of congo red was injected into a series of rabbits. The animals were killed one-half, one, two, twenty-four and forty-eight hours later. In none of them was there even a trace of vital staining. The congo red was excreted chiefly through the liver into the bile. Since the dye did not appear in the Kupffer cells their rôle in eliminating it was undetermined.

Saxl and Donath [5] reported the results of using a fine emulsion of fat which is put on the market under the trade name of oleokoniol. The fat droplets were so small that they passed through the finest capillaries. The emulsion was given intravenously, and the disappearance of the droplets was followed in the dark field. This method was used by Memmesheimer in his studies on the influence of arsphenamine on the reticulo-endothelial system. Our observations, also, are based on it.

---

* From the Department of Pathology of the University of Illinois College of Medicine.

1. Adler, H., and Reimann, F.: Ztschr. f. d. ges. exper. Med. **47**:617, 1925.
2. Wilensky, L. J.: Ztschr. f. d. ges. exper. Med. **54**:257, 1927.
3. Schellong: Med. Klin. **22**:1711, 1926.
4. Smetana: Bull. Johns Hopkins Hosp. **37**:383, 1925.
5. Saxl, P., and Donath, F.: Wien. klin. Wchnschr. **38**:66, 1925.

METHOD

Oleokoniol [6] was introduced by A. Neumann. It is a 20 per cent emulsion of fat, the droplets of which are slightly larger and more radiant in the ultramicroscope than hematokonia. In several batches, we found differences in the stability of the emulsion. Some of the samples were white and others were light yellow. Only the latter could be used. The droplets of the white emulsion do not appear in the peripheral blood. They fuse to larger drops in the capillaries of the lung where they are filtered off. Most of the yellow emulsion passes the capillaries of the lung and can be demonstrated in drops of peripheral blood. The injections are absolutely harmless; the dose for adult human beings is 5 cc., and for animals 0.2 cc. per kilogram of body weight. In normal human beings and animals, the droplets disappear from the blood within from five to six minutes. The disappearing time is constant and is not influenced by the pulse rate. In order to avoid hematokonia, the test is made in the morning before breakfast. We have counted the droplets in relation to the red blood cells, a square microscopic field being obtained by putting a rectangular diaphragm in the eye-piece. With some practice, blood drops of even size can be secured from the finger or the ear. They are carefully spread between slide and cover glass. Fields containing from four to five red cells are selected, and the droplets are counted in ten such fields. The average of the ten counts is taken. We have repeatedly checked our counts with satisfactory results. As the droplets sometimes reappear, it is necessary to follow them for at least ten minutes, a sample being taken each minute.

MICROSCOPIC EXAMINATION

Saxl and Donath described the storage of the emulsion in all parts of the reticulo-endothelial system. Staining with sudan III is not sufficient to determine the distribution of the fat emulsion in the body, since fatty substances may preexist. The injected fat, however, can be distinguished from the body lipoids by special stains. It gives a deep violet color with nile blue sulphate, is not double refracting and is negative to the Lorrain Smith stain with potassium bichromate hematoxylin.

When the emulsion of fat is injected into the vein of a rabbit and the animal is killed five minutes later, most of the fat is found in the liver. It has been engulfed by the Kupffer cells, especially in the periphery of the acini. The Kupffer cells quickly transmit the fat to the liver cells. Where a fat filled cell touches the capillary wall, a clear space becomes visible between the wall and the adjacent liver cell. Into this space the droplets pass over. They accumulate later in the

6. Manufactured by the Chemosan Company of Vienna.

periphery of the liver cells (fig. 1). Twenty minutes after the injection, the liver cells in the outer zone of the acini are filled with fat droplets of different sizes. The fat content of the Kupffer cells gradually decreases, and after twenty-four hours little fat is found in them, while the parenchymatous cells still contain an appreciable amount. Sections taken from the liver after forty-eight hours do not show any fat.

Some of the emulsion is deposited in the capillaries of the lung. It is seen in small circumscribed areas from which it is removed within twenty-four hours by perivascular histocytes which migrate with the fat droplets into the alveolar spaces. Little fat is found in the spleen. It is located free or inside of macrophages in a zone about the malpighian

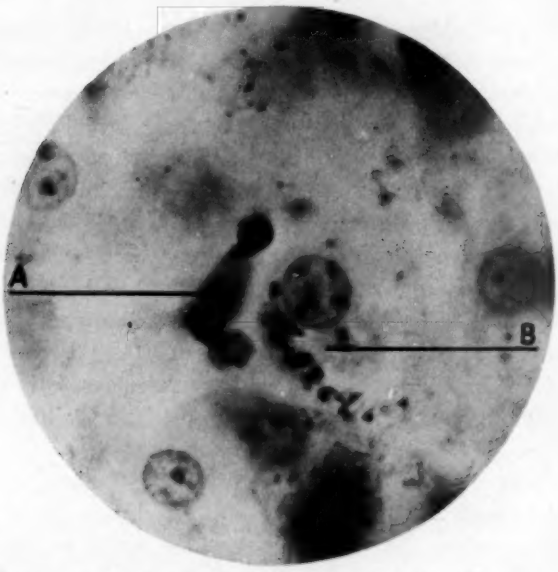


Fig. 1.—Liver of rabbit injected with 2 cc. of the emulsion of fat and killed twenty minutes later. Frozen section, sudan III, hematoxyline. *A* indicates Kupffer cell filled with fat droplets; *B*, liver cell containing fat globules in the part adjacent to the portal capillary. Magnification; × 1,500.

bodies. There is not any storage by the phagocytic cells of the bone marrow, lymph glands, suprarenals, etc. A more marked phagocytosis of the fat by the histocytes of the spleen is observed when large amounts of the emulsion are given. Under this condition the oil droplets circulate in the blood for hours and it seems as if the eliminating apparatus of the liver has been saturated.

EXPERIMENTAL STUDIES

The Effect of Splenectomy and Evisceration on Disappearing Time of the Emulsion.—A dog, weighing 6 Kg., was splenectomized, and

1.5 cc. of the oil was injected into the femoral vein two hours later. The results of this experiment are given in figure 2.

There was not any difference in the disappearing time of the emulsion before and after the operation.

In a dog, weighing 9 Kg., the spleen, pancreas and entire intestine were removed and the hepatic vessels were ligated. Dextrose solution was infused continuously. Two and one-half hours after the operation the dog was in good condition and 2 cc. of the emulsion was injected.

While before the operation the droplets had disappeared from the blood within five minutes, there was little change in their number after the evisceration for the entire period of the observation. The slight decrease during the first few minutes was apparently due to the removal of some of the fat by the lung. In this animal, the bone marrow and

Fig. 2.—Splenectomy performed in dog weighing 6 Kg. *A*, test at 10:33 a. m., 1.5 cc. oil; *B*, test two hours after splenectomy.

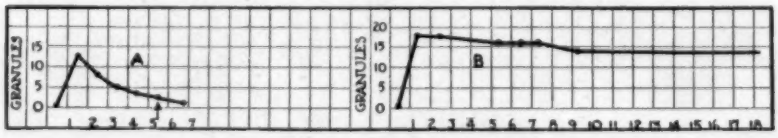


Fig. 3.—Eventration experiment on dog weighing 9 Kg. *A*, test at 9 a. m., 2 cc. of emulsion intravenously; *B*, test two and one half hours after removal of the abdominal viscera (spleen, pancreas and gastro-intestinal tract; ligation of all hepatic vessels); infusion of dextrose intravenously; 2 cc. of emulsion intravenously.

a large part of the lymphatic tissue were left intact. They did not have any effect on the oil droplets that were circulating in the blood.

These experiments were repeated with identical results and the microscopic observations were confirmed. As far as the removing of the emulsion is concerned, the liver is the most active part of the reticulo-endothelial system. From the histologic picture it is also evident that the function of the Kupffer cells cannot be separated from that of the liver cells; both cells are a functional unit. With the emulsion, therefore, we test the liver, particularly the relations between its phagocytic and parenchymatous tissue.

The Influence of Thyroidectomy on the Disappearing Time of the Emulsion.—Ascher,[7] Furuya [8] and Bierstein and Rabinowitsch [9] showed that the phagocytic activity of the polymorphonuclear leukocytes is influenced by the glands with internal secretion. Especially in thyroidectomized animals, the phagocytosis is markedly diminished. The feeding of thyroid substances restores the phagocytic power of the cells. According to Ascher, the macrophages, too, are less active after the thyroid has been removed. While Bierstein and Rabinowitsch believed that the changes are located in the cells, Ascher and Furuya found evidences that the effect is indirect by way of the serum.

The studies of Mandelstamm,[10] Louros and Scheyer,[11] and Goldzieher and Hirschhorn [12] pointed toward the possibility of hormone

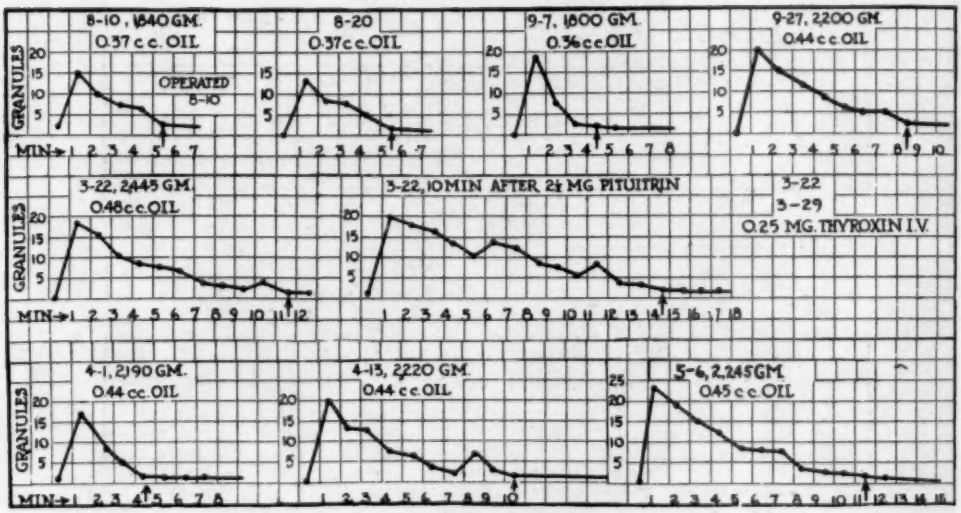


Fig. 4.—Removal of thyroid in rabbit 100.

stimulating or depressing the functional activity of the reticulo-endothelial system. Goldzieher and Hirschhorn found, for instance, that injections of thyroid preparations decrease the storage of cholesterol Morphologic examinations alone, however, are not sufficient.

A series of five rabbits, weighing from 1,400 to 2,000 Gm., were thyroidectomized, and the disappearing time of the emulsion was deter-

7. Ascher, L.: Klin. Wchnschr. **3**:308, 1924.
8. Furuya, K.: Biochem. Ztschr. **147**:410, 1924.
9. Bierstein and Rabinowitsch: Klin. Wchnschr. **4**:2013, 1925.
10. Mandelstamm: Virchows Arch. f. path. Anat. **261**:702, 1927.
11. Louros, N., and Scheyer, H. E.: Ztschr. f. d. ges. exper. Med. **55**:702, 1927.
12. Goldzieher, M. A., and Hirschhorn, L.: The Reticulo-Endothelial System, Arch. Path. **4**:958 (Dec.) 1927.

mined at intervals of from two to four weeks. The details of an experiment are shown in figure 4.

During the first month after the operation there is no change in the time required for removing the oil droplets. A slight, but distinct delay is first noted about the seventh week. The delay gradually becomes more and more pronounced, and after several months the droplets remain in the blood more than twice as long as they did before the thyroidectomy. The injection of pituitary extract prolongs the disappearing time still more. Thyroxin, on the other hand, causes a quick restoration of normal conditions, which is of but short duration, since after two weeks its effect is gone. The same dose of thyroxin

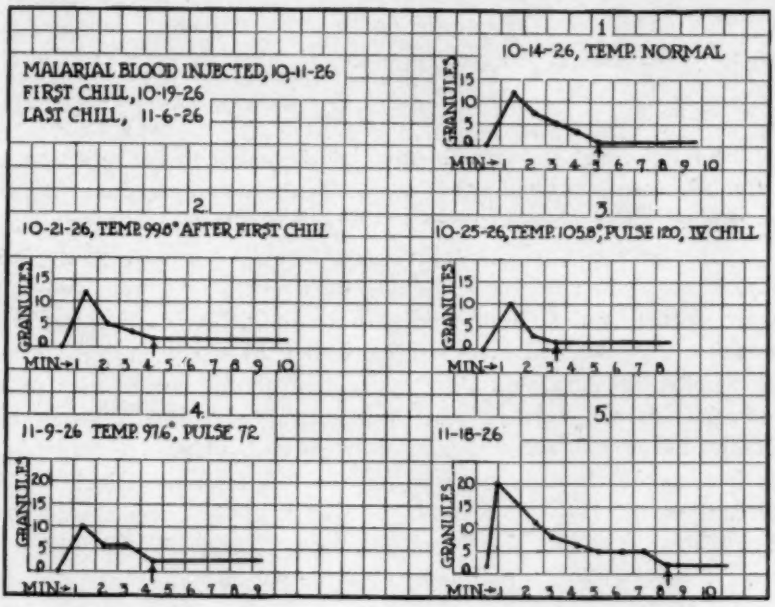


Fig. 5.—Malaria treatment for taboparesis in John P., aged 49.

does not influence the rate of storage in normal adult rabbits while in young animals, there is sometimes a slight increase in the speed.

These experiments demonstrate that the lack of the thyroid interferes with the quick elimination of the fat droplets through the liver. It may be recalled here, that Saxl and Donath described a shortened disappearing time of the emulsion of fat in patients with exophthalmic goiter.

Observations on Malaria in Human Beings.—In a number of normal persons the function of the liver was determined with the aid of the emulsion. Little differences were found, from five to six minutes being required for the elimination of the fat globules. In certain pathologic

conditions deviations from the normal were observed, but the number of cases was too small to allow conclusions. Only the results on three patients with tertian malaria will be described, because they are clearcut. The patients were suffering from general paralysis and had been inoculated with blood from patients with malaria.

During the chill in malaria, a distinct increase is observed in the functional activity of the liver. The disappearing time of the oil globules drops from five to three minutes. In this case the decrease still was evident on the third day after the last chill. Nine days later, however, the liver was less active than normally, eight minutes being necessary for clearing the blood of the emulsion. In another patient the delay was manifest two days after the last attack. He had received 90 grains (5.85 Gm.) of quinine and a slight degree of jaundice was present at the time of the test. Quinine by itself is without effect.

CONCLUSIONS

The relations of the reticulo-endothelial system to the other tissues of the body are so intimate that it is difficult to analyze their function separately. This is demonstrated by the function test with the emulsion.

Fat droplets so small that they pass the blood vessels of the lung without fusing together and blocking them are quickly removed from the circulation by the Kupffer cells of the liver. It is only after their saturation that the histocytes of the spleen take part in the storage. The Kupffer cells transmit their fat content almost immediately to the liver cells. Hence, both cells act as a functional unit. A penetration of the capillary wall and a deposition in parenchymatous cells of larger fat droplets of the size of erythrocytes has been described by Del Baere.[13]

Schellong says that the liver function tests with the colloidal dyes do not depend only on the integrity of the parenchymatous cells since changes in their elimination also may be due to an alteration of the stellated cells. The experience with the oil emulsion is in accord with his conception.

What do the liver cells do with the fat droplets which they have received from the Kupffer cells? The histologic observations seem to indicate that they destroy them since they do not appear in the bile or elsewhere in the body.

Morphologic and experimental observations suggest the use of the emulsion as a functional test of the parenchymatous and phagocytic cells of the liver, especially of their relations to each other. There is a marked slowing of the elimination of the injected fat globules following removal of the thyroid. It takes several weeks before this

13. Del Baere, L. J.: Nederl. Maandschr. v. Geneesk. **13**:644, 1926.

effect becomes manifest. Thyroxin stimulates the function of the liver in thyroidectomized animals. Of the other hormones, an inhibitory effect of the pituitary extract is mentioned, which can also be demonstrated on human beings. Epinephrine hydrochloride may stimulate or depress, and there are interesting individual differences. The action of insulin on normal persons is insignificant.

During chills in malaria, the activity of the liver is increased; this can be inferred from the marked decrease of the disappearing time. When the chills are over, a transient inhibition of the liver follows sooner or later.

SUMMARY

Congo red is excreted through the liver, but is not stored by the histocytes.

A fine emulsion of fat can be used as a liver function test, but not as a test of the reticulo-endothelial system.

A function test of the reticulo-endothelial system still is lacking.

NONSPECIFIC DESENSITIZATION*

M. L. ISAACS, PH.D.
NEW YORK

Anaphylactic shock may be prevented by specific or nonspecific means. The specific method involves the use of the antigen to which an animal has been sensitized: the principles underlying the process seem to be relatively simple, and the phenomenon is easily demonstrated. Nonspecific desensitization, on the other hand, presents a much more complicated picture. The substances and methods classed as nonspecific are many in number and most diverse in character. The desensitization itself, furthermore, appears to be dependent on several factors which as yet have failed to receive proper recognition. As a consequence, the literature contains many conflicting data, based, in many cases, on what seem to be identical experiments.

In order to discover the nature of these variables, I have attempted to analyze and, as far as possible, classify some of the available data. In doing this, any reference to the various theories that have been put forward has been avoided. The reasons for this will appear obvious when the uncertainty of the data as a whole is considered. Some discussion of the theoretical side is given in a review of anti-anaphylaxis by Longcope.

The material collected was limited to that in which the guinea-pig was the test animal, although some work has been reported on dogs and pigeons. Clinical data on desensitization are also not lacking, but as each case represents so many factors which are beyond experimental control, such material has not been included. One is impressed, however, with a general similarity in comparing experimental work on guinea-pigs with attempts at desensitization in human beings.

THE METHODS OF TESTING DESENSITIZATION

In testing for desensitization in guinea-pigs, one method has been used almost exclusively. This involves the injection of the material in question a short time previous to a normally fatal quantity of antigen. If the animals survive, they are said to be desensitized. This procedure will be referred to as the "survival method." Although the test animals may exhibit markedly anaphylactic symptoms, these are of relatively brief duration. As will be pointed out, some animals of a group may succumb, in a manner exactly as if preventive treatment had not been given.[1]

---

*From the Departments of Bacteriology and of Sanitary Science. College of Physicians and Surgeons, Columbia University.

1. About 20 per cent of the control animals recover (Auer and Lewis, Lumière and Courturier and Karsner and Ecker). A control animal which survives usually exhibits marked symptoms for one or two hours.

Other methods which have been employed to detect desensitization include the use of skin reactions, temperature measurements, uterine strip contractions and perfusion experiments. These methods do not seem to give results which parallel those of the survival method. Kopaczewski and some others have added various substances to serum and noted the effect on the production of anaphylatoxin in vitro. If the quantity was reduced, the process was called "desensitization," but such a "desensitization" bears a remote relation, if any, to the subject of this paper.

THE DESENSITIZING AGENTS

The substances and methods which produce desensitization are both numerous and of great chemical variety. At present there apparently is no satisfactory classification. Some attempt has been made to establish two groups: those substances which merely suppress symptoms and those which actually desensitize. Amyl nitrite (Kopaczewski, third reference), urethane and chloralose (Besredka, third reference) are clearly of the former. Anesthetics are also classed in the first group, but in their case the classification is not quite so definite. Kopaczewski, Roffo and Roffo, for example, found that quantities of ether and chloroform too small to produce anesthesia were capable of desensitizing. We have, therefore, included all the materials which have been reported as producing desensitization in one alphabetical list.

Substances Which Have Been Reported as Producing Nonspecific Desensitization

Alcohol (Besredka, third reference; Cruveiheir)

Alocaine hydrochloride (Lumière and Elselme)

Amyl nitrite (Kopaczewski, third reference)

Anaphylactic shock, heterologous (Gay and Southard; Bessau; Wells and Osborne; Bessau, Opitz and Preusse; Lumière and Courturier)

Atropine (Auer and Lewis; Anderson and Schultz; Stoland and Sherwood; Zunz and La Barre, second reference)

Barium chloride (Biedl and Kraus)

Bayer 205 (Collier)

Calcium chloride (Besredka; Belin)

Calcium lactate (Kastle)

Camphorated oil [camphor liniment] (Kopaczewski, fourth reference)

Cephalin (Karsner and Ecker, second reference)

Chloral hydrate (Anderson and Schultz; Anderson and Rosenau; Banzhaf and Famulener)

Chloralose [chloral hydrate and dextrose preparation] (Besredka, third reference)

Chloroform (Kopaczewski, Roffo and Roffo)

Choline (Zunz and La Barre)

Dyes, fluorescent (Girard and Peyre)

Ether (Besredka, third reference; Kopaczewski, Roffo and Roffo)

Ethyl chloride (Besredka, third reference)

Epinephrine (Anderson and Schultz)
Gum arabic [acacia] (Manwaring)
Hirudin (Zunz and Bernard)
India ink (Moldovan and Zolog; Jungeblut and Berlot, first reference)
Lanolin [hydrous wool fat] (Fujioka)
Lipoids of serum and egg (Jobling and Petersen)
Manganous chloride (Pico)
Mineral waters (Arloing et al; Henrijohn and Kopacezwski)
Ovolecithin (Achard and Flandrin)
Oxygen (Anderson and Schultz)
Orange juice (Wedgewood)
Pilocarpine (Lévy-Solal and Tzanck)
Proteins, serums and protein decomposition products (Besredka; Calvary; Karsner and Ecker; Kellaway and Cowell; Manwaring; Isaacs)
Peptone (Biedl and Kraus; Pfeiffer and Mita; Friedberger and Kumagai)
Reduced air pressure (Lumière and Courturier, second reference)
Soap[2] (Jobling and Petersen)
Sodium carbonate (Kopaczewski; Sicard and Paraf)
Sodium chloride (Friedberger and Hartoch; Armand-Delille and Launoy; Richet)
Sodium formaldehyde sulphoxylate (Brodin and Huchet)
Sodium hyposulphite[2] (Lumière and Chevrotier)
Sodium iodosobenzoate and related compounds (Amberg and Knox)
Sodium oleate (Kopaczewski and Vahram)
Starvation (Lesné and Dreyfus; Konstantoff; Pierrot and Crampon)
Stovaine (Kopaczewski)
Sulphur, colloidal (Arloing, Langeron and Ricard)
Syphilitic antigen of Bordet (Duprez)
Tetanus toxin (Billard and Barbes)
Trypanosome infection (Hartoch and Sirenskij)
Urethane (Besredka, third reference)
Venoms (Billard and Barbes)

The tabulation lists such widely differing materials that one might easily suppose that all substances are capable of producing desensitization.[3] The following, however, have been reported as being without effect: Congo red, glycogen or dextrin (Karsner and Ecker, second reference); calcium acetate, magnesium sulphate, nitrites or pancreatin (Anderson and Rosenau); morphine or opium extracts (Besredka, third reference); certain mineral waters (Chassevant); thorium X (Corper); roentgen rays (Corper, Black and Moore); trypan blue (Isaacs, second reference), and olive or almond oils (Jobling and Petersen). Hyde and Reed and Lamson found that heparin does not desensitize guinea-pigs, although it prevents shock in pigeons. Water and physiologic sodium

2. As this substance is added to the antigen before injection, it may conceivably not be a desensitizing substance.

3. It would be of interest to know the effect of each of the materials on alexin. The work of Jungeblut and Berlot on India ink seems to show a close parellelism between desensitization and the reduction of circulating alexin.

chloride solution appear to be without effect on shock. Besides these materials, many listed in the tabulation have been used without success by some investigators.

An increase in sensitivity follows the use of quinine (Smith) or cyanide (Amberg and Knox).

THE EFFICIENCY OF DESENSITIZATION

We have mentioned the fact that when the survival method is used, not all the treated animals appear to be desensitized. Some die as quickly and as violently as the untreated controls. The percentage of recoveries ranges from 50 to 100 per cent. It would appear that with most

TABLE 1.—*Percentage of Animals Desensitized by Various Substances*

Substances Used	Per Cent
Anaphylactic shock (Bessau)	90
Atropine sulphate (Anderson and Schultz)	30
Atropine sulphate (Auer and Lewis)	85
Cephalin	85
Chloral hydrate (Anderson and Schultz)	40
Chloral hydrate (Banzhof and Famulener)	75
Chloral, urethane and oxygen combined (Anderson and Schultz)	65
India ink (Moldovan and Zolog)	100
India ink (Jungeblut and Berlot)	50
Manganous chloride	35
Mineral waters (Henrijohn and Kopaczewski)	50
Ovolecithin	100
Oxygen	45
Peptone (Karsner and Ecker)	65
Reduced air pressure	70
Seed extracts	50
Serum (Karsner and Ecker) intravenously	65
subcutaneously	50
Serum lipoids	75
Soaps (added to antigen)	100
Sodium chloride	50
Sodium formaldehyde sulphoxylate (added to antigen)	90

methods, nonspecific desensitization is 50 per cent efficient. The data are summarized in table 1.

The figures given in table 1 are only approximate. Some represent many animals, others few. The experiments in some cases were carried out under widely differing conditions, although in general one minimum lethal dose of antigen was used as the shock injection. The data are indicative but not conclusive. There are two conclusions, however, which they certainly justify:

1. Any given procedure may fail to desensitize all the animals used in an experiment.

2. It is absolutely necessary to work with a large number of animals. This is a corollary to the preceding statement.

The last conclusion is emphasized in the work of Karsner and Ecker.

THE PERIOD OF INDUCTION

After the injection of a material under test, some time is required for the desensitization to develop. This has been a tacit assumption on the part of most workers, because they have tested out the effect of desensitization after from 6 to 24 hours. That such a period is necessary is suggested by the fact that such complex mixtures as milk and serum may be used to produce anaphylaxis, although they contain non-antigenic substances capable of preventing shock. The induction period has been most carefully studied by Kellaway and Cowell, who employed uterine strips taken from animals that received a desensitizing injection and were slaughtered at varying intervals. The results indicated that desensitization begins at the end of fifteen minutes; is clear at the end of thirty, and is established after one hour. Calvary, using the survival method with heterologous serum, obtained similar results. In the experiments of Achard and Flandrin, ovolecithin saved two of four animals when injections were made thirty minutes before, and all of eleven animals when injections were administered two hours before a shock injection. Moldovan and Zolog found that india ink was without influence at the end of eight minutes, but effective after one hour. In a few cases shorter periods have been reported. Thus, pilocarpine is said to protect immediately, choline in fifteen minutes and hirudin in thirty. In general, however, it appears that desensitization requires one hour to reach a protective level.

DURATION OF THE DESENSITIZED STATE

Nonspecific desensitization is of short duration. It appears that with most agents employed, full sensitivity returns at the end of twenty-four hours. Karsner and Ecker (first reference) found that with sheep serum injected into animals sensitized to horse serum, at the end of twenty-four hours, four of five were desensitized; at the end of seventy-two hours, four of seven, and at the end of 120 hours, three of five. With human serum, two tried after seventy-two hours were saved, but after a lapse of 120 hours, two of five animals in which the injections were made died. Kellaway and Cowell, using smooth muscle contraction as an indicator of desensitization, observed a complete return of sensitivity after six hours. Using the survival method, however, it appeared that desensitization lasted at least twenty-two hours. Alcohol prevents shock for twenty-four hours, choline for twenty-five minutes, and hirudin for four hours. The effects of india ink, according to the work of Moldovan and Zolog, last for fifteen days. Lumière and Courturier found that guinea-pigs sensitized to egg white and horse serum and desensitized to egg white were also unresponsive to horse serum for not more than twenty hours. Bessau, some years before, tried a similar experiment and reported a desensitization lasting several days.

The data just given are not extensive, since most investigators have chosen some arbitrary time between one and twenty-four hours. The conclusion seems justified, however, that nonspecific desensitization is of short duration, returning in many cases within one day after the giving of the protective injection.

THE INTOXICATING DOSE OF ANTIGEN

One of the most essential factors is the quantity of antigen used for the intoxicating injection. Thus, while many substances will desensitize an animal to one minimum lethal dose of protein, few will desensitize it to four times this dose, and none, so far as the literature shows, to six times the normally fatal quantity. Table 2 summarizes what data I have been able to gather on this subject:

Unfortunately, the data in table 2 represent few animals, so that the conclusion reached is not one of absolute certainty. However, the

TABLE 2.—*Multiple of Minimum Lethal Dose of Antigen Safely Supported*

Desensitizing Substance	Multiple
Choline	1+
Hirudin	1+
India ink (Moldovan and Zolog)	4
Lipoids of serum and egg	2
Peptone (Friedberger, Kumagai and Odaira)	4
Serum (Friedberger and Szymanowski)	1
Soaps (added to antigen)	5
Sodium chloride (Armand-De Lille)	1
Starvation (Konstantoff)	4+

minimum lethal dose of antigen is to be borne in mind in testing the efficacy of any desensitizing agent.

THE QUANTITY OF DESENSITIZER

The size of the desensitizing dose may also be of importance. At present there is some definite evidence, that, at least for some desensitizing substances, there exists a definite quantity with which the best results are obtained. Arloing has concluded that small doses of colloidal sulphur are more efficacious than large ones, and a similar conclusion has been suggested for injections of cephalin by Karsner and Ecker. My own work, although not extensive along this line, suggests the same possibility with seed extracts. Arloing, Langeron, Milhaud and Ricard, using mineral waters, recently found that the optimal desensitizing injection lies between 2 and 6 cc. Smaller quantities were without effect, while larger ones appeared to augment the shock. Such a condition may explain the failure of Larsen and others to desensitize with peptone, a material with which others have succeeded by using much smaller doses. It must be concluded tentatively that the size of the desensitizing injection may have a great bearing on the success or failure of an experiment.

NUMBER OF DESENSITIZING INJECTIONS

It is not definitely known whether several desensitizing injections give rise to a better desensitization than one. Karsner and Ecker found some evidence to favor the conclusion that one injection is about as effective as several, and I have some data of a similar nature. (Several injections of protein are well proved to be more effective in specific desensitization). A double administration of chloral hydrate was more effective than a single one in desensitizing guinea-pigs (Banzhaf and Famulener). Arloing and others found that with mineral waters at least eleven injections are necessary. No one seems to have tried such a large number with other substances.

OTHER FACTORS

What other factors may be concerned in desensitization can only be suggested. Diet, for example, may have a considerable influence. Wedgewood found that guinea-pigs on a scorbutic diet succumbed more quickly on second anaphylactic injection, than those on a diet rich in vitamins. It would therefore seem probable that if sensitized guinea-pigs were fed a scorbutic diet and injected with a given desensitizing substance their chances of recovery would be slight. (Zolog recently showed that guinea-pigs which are already scorbutic are difficult to sensitize). Wedgewood and Grant found that injections of protein, ordinarily incapable of causing anaphylaxis in rats, may produce shock if vitamin B is absent from the diet.

The effect of disease may also have an important bearing. I found that pigs which were suffering from distemper were not desensitized by a procedure which desensitized normal guinea-pigs. (Desensitization proceedings may, therefore, be contraindicated in the presence of certain diseases.) On the other hand, as Hartoch and Sirenskij have shown, it is possible for an infection to prevent anaphylactic shock.

The hydrogen ion concentration of the various solutions used, the volume of the solutions used, the rates of injection and the "degree" of sensitization of the guinea-pigs—all probably have some influence on the results, but there is to my knowledge, no data on these subjects.

SPECIFIC AND NONSPECIFIC DESENSITIZATION

This article has dealt entirely with nonspecific desensitization. A brief comparison with specific desensitization may be of interest. Deductions may be most easily drawn from the work of Karsner and Ecker and of Calvary, although these workers have used serums alone. Both types of desensitization require a period of induction which appears to be about one hour. Both types are of finite duration, although the specific desensitization may last for several weeks, as against one day

for the nonspecific. The specific is much more efficient than the nonspecific method in that almost 100 per cent of the animals are desensitized by the first as compared to about 50 per cent by the second type of procedure. It must be remembered, however, that several injections of the specific protein are usually used. Both methods compare in their failure to protect to several times the intoxicating injection of antigen. Finally, specific desensitization produces more or less of a shock, whereas nonspecific injections are usually without such effect.

COMMENT ON SOME OF THE CONFLICTS

The value of many of the materials used has been called into question. Four interesting examples may serve as illustrations:

Peptone.—The greatest difference of opinion exists as to the usefulness of peptone. The most obvious reason for this is that the term "peptone" is used to cover a great variety of chemically different substances, and even in a given brand, variations often are found. Added to the confusion caused by the lack of an exact definition is the failure on the part of some workers to take into account the facts which have already been brought out. Anderson and Rosenau (1908) appear to have been the first to have tried the effect of peptone on anaphylaxis. They found that it did not exert any influence on anaphylactic shock. The details of their experiments are not given. Biedl and Kraus next used peptone and concluded that it was capable of desensitizing. Their article, however, does not contain any data. Shortly thereafter, Pfeiffer and Mita, using temperature reactions, found that after the intraperitoneal injection of peptone, sensitized guinea-pigs did not respond with a rise in temperature when treated with antigen. This refractory condition lasted for twelve days. Few animals were used, however. Besredka, Strobel and Jupille killed one guinea-pig which had been sensitized to horse serum, treated with peptone and, finally, shocked with horse serum. Their dose of horse serum was large. Karsner and Ecker (second reference), using Witte's peptone, saved about 50 per cent of the animals treated. Peptones recently were used with much success by some in the treatment of patients with allergy (Rolleston). Others have been unsuccessful. Larsen and co-workers tried the effect of peptone (a mixture of Armour's and Witte's) on anaphylaxis in guinea-pigs with the view of deciding whether or not the use of peptone had any justification in the treatment of disease. Unfortunately, they did not vary their experiments sufficiently and probably used too large a quantity of peptone and waited too short a time for it to take effect. They also tried the effect of adding peptone to a Dale bath, but as this method has not been used for other desensitizing substances except atropine, it cannot be said *a priori* that it would measure

desensitization. More data are much needed. As has been pointed out by others, the ease of sterilization and the lack of antigenic properties make peptone almost ideal for nonspecific treatment.

Calcium Chloride.—As early as 1906, Netter reported favorably on calcium chloride for the prevention of serum sickness. Of 258 children who took calcium chloride previous to injections of antitoxin 2.38 per cent developed eruptions. In an equal number of children who did not take the salt the percentage of failures was 15.53. Anderson and Rosenau and Biedl and Kraus tested out the effect of calcium chloride on anaphylaxis of guinea-pigs and concluded that it exerted no effect. Details were not given. A possible explanation of the situation lies in the work of Belin, who found that if calcium chloride was given some time before the shocking dose of antigen, the shock was attenuated; if given during the shock the symptoms actually seemed to be increased. Besredka also found that calcium chloride given before the shock had a preventive effect.

Anaphylactic Shock.—In 1907, Rosenau and Anderson reported some work intended to show the specificity of anaphylaxis. Gay and Southard immediately pointed out that, although the original authors concluded to the contrary, their tables showed some evidence that one anaphylactic shock would prevent a second with another protein. Their own data, based on experiments with guinea-pigs sensitized to three antigens, also brought out this fact. The article of Wells and Osborne contained similar data. Using the method of testing out with local reactions, Bessau, Opitz and Preusse found that guinea-pigs sensitized to two antigens and intoxicated with one were nonsensitive to the other for a period ranging between one and three days. The full sensitization returned between five and eight days. Lumière and Courturier (first reference), working with guinea-pigs and using the survival method, concluded that with a double sensitization and shock to one protein, a desensitization to the other was produced, which lasted for not more than twenty hours. There does not seem to be any question, then, that anaphylactic shock desensitizes, the process, however, being subject to the factors which I have already pointed out.

India Ink.—Moldovan and Zolog were the first to report that india ink prevented shock. In a later article (second reference) they stated that not all samples of india ink acted alike. One would naturally conclude, although the authors did not, that some other substance besides the colloidal carbon must be the effective agent. This may explain the observation of Simitch who recently concluded that india ink was without effect on anaphylaxis. Jungeblut and Berlot, working under carefully controlled experimental conditions, were able to show a 50 per cent survival.

CONCLUSIONS

From my analysis of the material, certain conclusions are suggested. It must be borne in mind that the evidence presented was not decisive in any case. The following statements are, therefore, to be regarded as requiring more proof before they are established. They may serve best as precautions which must be observed in future work in this field.

1. Nonspecific desensitization is effective in about 50 per cent of the animals (guinea-pigs) used in an experiment. Many animals must be used to make certain that chance does not make a given material seem more efficacious than it really is.

2. Desensitization develops gradually, requiring, in many cases, at least one hour to reach a protective level.

3. Nonspecific desensitization is of short duration—probably not more than twenty-four hours.

4. Desensitization may be produced to one lethal dose of antigen but not to five.

5. The quantity of desensitizer is probably of importance also, instances being recorded in which smaller doses seemed more efficacious than larger doses.

6. The advantage of several desensitizing injections over a single inoculation has not been demonstrated except for one or two substances. This is a matter deserving of more attention.

7. Other factors which may influence desensitization are diet and disease.

ANAPHYLAXIS AND DESENSITIZATION IN HUMAN BEINGS

Much has been written on the subject of anaphylaxis and desensitization in human beings. Specific desensitization has been much used, but in cases in which the protein antigen is unknown, nonspecific procedures must, of course, be resorted to. Many substances have been tried in the production of nonspecific desensitization, all of which have also been used with guinea-pigs.

The application of these conclusions is obviously of great importance, if future work continues to develop the close parallelism which appears to exist between anaphylaxis in guinea-pigs and anaphylaxis in human beings. Thus it would seem that most nonspecific substances must be injected some time before the injection of a protein to which a person may be sensitive, or before the oncoming of an allergic attack. If the injection was administered during an attack beneficial results could not be expected. Furthermore, the injections probably must not be made too far in advance. Other factors, already pointed out, which must be borne in mind, are the size of the desensitizing injection and the possible presence of certain diseases which may contraindicate desensitization

proceedings. A person who is "desensitized" may not be injected with large quantities of such materials as horse serum, with impunity. Finally, if the analogy is complete, one can hardly hope to find a procedure which will be successful in all cases. Many physicians are of the opinion that nonspecific treatments are successful in about two thirds of their cases.

BIBLIOGRAPHY

Achard, C., and Flandrin, C.: Compt. rend. Soc. de biol. **71**:91, 1911.

Amberg, S., and Knox, J. H. M.: Influence of Sodium Iodoxybenzoate on Reactions of Inflammatory Character, J. A. M. A. **59**:1598 (Nov. 2) 1912.

Anderson, J. F., and Schultz, W. H.: Proc. Soc. Exper. Biol. & Med. **7**:32, 1909.

Anderson, J. F., and Rosenau, M. J.: J. M. Research **19**:41, 1908; **21**:1, 1909.

Arloing, F.; Langeron, L., and Milhaud and Ricard: Compt. rend. Soc. de biol. **89**:1296, 1923.

Arloing, F.; Langeron, L., and Ricard: Compt. rend. Soc. de biol. **90**:221, 1924.

Arloing, F., and Vauthey, P.: Compt. rend. Soc. de biol. **86**:687, 1922.

Armand-Delille, P., and Launoy, L.: Compt. rend. Soc. de biol. **72**:61, 1912.

Auer, J., and Lewis, P. A.: Acute Anaphylactic Death in Guinea-Pigs, J. A. M. A. **53**:458 (Aug. 7) 1909.

Banzhaf, E. J., and Famulener, L. W.: J. Infect. Dis. **7**:577, 1910.

Belin, M.: Compt. rend. Soc. de biol., 1913, vol. 74.

Besredka, A.: Compt. rend. Soc. de biol. **62**:1053, 1907; Ann. de l'Inst. Pasteur **21**:950 1907; Anaphylaxis and Anti-Anaphylaxis, St. Louis, C. V. Mosby Company, 1917.

Besredka, A.; Strobel, H., and Jupille, F.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **16**:249, 1913.

Bessau, G.: Zentralbl. f. Bacteriol. **60**:637, 1911.

Bessau, G.; Opitz, H., and Preusse, O.: Zentralbl. f. Bacteriol. **74**:162, 1914.

Biedl, A., and Kraus, R.: Wien. klin. Wchnschr. **22**:363, 1909.

Billard, G.: Compt. rend. Soc. de biol. **74**:99, 1913.

Billard, G., and Barbes, L.: Compt. rend. Soc. de biol. **74**:1320, 1913.

Brodin and Huchet: Compt. rend. Acad. d. sc. **173**:865, 1921.

Calvary, M.: München. med. Wchnschr. **58**:1442, 1911.

Chassevant, A. J.; Galup, J., and Delpech, J.: Compt. rend. Soc. de biol. **74**:679, 1913.

Collier, W. A.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **52**:191, 1927.

Corper, H. J.: J. Infect. Dis. **25**:248, 1919.

Corper, H. J.; Black, L. T., and Moore, M.: J. Infect. Dis. **30**:50, 1922.

Cruveilhier, L.: Compt. rend. Soc. de biol. **70**:124, 1911.

Duprez, C.: Compt. rend. Soc. de biol. **86**:285, 1922.

Friedberger, E., and Hartoch, O.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **3**:581, 1909.

Friedberger, E., and Szymanowski, W.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **14**:381, 1912.

Friedberger, E.; Kumagai, T., and Odaira: Ztschr. f. Immunitätsforsch. u. exper. Therap. **14**:391, 1912.

Fujioka, N.: Japan. M. World **5**:319, 1925.

Gay, F. P., and Southard, E. E.: J. M. Research **19**:5, 1908.

Girard, P., and Peyre, E.: Compt. rend. Soc. de biol. **188**:84, 1926.

Hartoch, O., and Sirenskij, N.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **12**:85, 1912.

Henrijohn, F., and Kopaczewski, W.: Compt. rend. Soc. de biol. **92**:192, 1925.
Hyde, R. R.: Am. J. Hyg. **7**:614, 1927.
Isaacs, M. L.: M. Bull. Univ. Cincinnati, 1924, p. 181; Proc. Soc. Exper. Biol. & Med. **23**:185, 1925.
Jobling, J. W., and Petersen, W.: J. Exper. Med. **20**:468, 1914.
Jungeblut, C. W., and Berlot, J. A.: J. Exper. Med. **43**:129, 1926; **43**:797, 1926.
Karsner, H. T., and Ecker, E. E.: **30**:333, 1921; **34**:636, 1924.
Kastle, J. H.; Healy, D. J., and Buckner, G. D.: J. Infect. Dis. **12**:127, 1913.
Kellaway, C. H., and Cowell, S. J.: Brit. J. Exper. Pathol. **3**:268, 1922.
Konstantoff, S.: Compt. rend. Soc. de biol. **72**:262, 1912.
Kopaczewski, W.: Compt. rend. Soc. de biol. **82**:836, 1919; **83**:837, 1920; Ann. de méd. **8**:291, 1920; Compt. rend. Acad. d sc. **172**:1386, 1921.
Kopaczewski, W.; Roffo, A. H., and Roffo, H. L.: Compt. rend. Acad. d. sc. **170**:1409, 1920.
Kopaczewski, W., and Vahram, A.: Compt. rend. Acad. d. sc. **169**:250, 1919.
Larsen, N.; Haigh, A. V. R.; Alexander, H. L., and Paddock, P.: J. Immunol. **8**:409, 1923.
Lesné and Dreyfus: Compt. rend. Soc. de biol. **71**:153, 1911.
Lévy-Solal and Tzanck: Presse méd. **31**:669, 1923.
Longcope, W. T.: Physiol. Rev. **3**:240, 1923.
Lumière, A., and Chevrotier, J.: Compt. rend. Acad. d. sc. **171**:741, 1920.
Lumière, A., and Courturier, H.: Compt. rend. Acad. d. sc. **173**:800, 1921; **176**: 1619, 1923.
Lumière, A., and Elselme, J.: Compt. rend. Acad. d. sc. **183**:578, 1926.
Manwaring, W. H.; Hosepian, V. M., and Thompson, W. L.: Anaphylactic Capillary Permeability, J. A. M. A. **82**:542 (Feb. 16) 1924.
Moldovan, J., and Zolog, M.: Compt. rend. Soc. de biol. **89**:1239, 1923; **92**:720, 1925.
Mougeout, A.: Compt. rend. Soc. de biol. **82**:191, 1919.
Netter, A.: Compt. rend. Soc. de biol. **60**:279, 1906.
Petersen, W. F.; Jaffe, R. H.; Levinson, S. A., and Hughes, T. P.: J. Immunol. **8**:367, 1923.
Pfeiffer, H., and Mita, S.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **6**:410, 1910.
Pico, C. E.: Compt. rend. Soc. de biol. **91**:1049, 1924.
Pierrot and Crampon: Compt. rend. Soc. de biol. **89**:1282, 1923.
Reed, C. I., and Lamson, R. W.: J. Immunol. **13**:433, 1927.
Richet, C.; Brodin, P., and Saint-Girons, F.: Compt. rend. Acad. d. sc. **169**:9, 1919; Rev. de méd. **37**:7, 1920.
Rosenau, M. J., and Anderson, J. F.: J. Infect. Dis. **4**:552, 1907.
Rolleston, H.: Brit. M. J. **2**:231 and 554, 1921.
Sicard and Paraf: Bull. et mém. Soc. méd. d. hôp. de Paris **45**:60, 1921.
Simitch, T. V.: Compt. rend. Soc. de biol. **94**:23, 1926.
Smith, M. I.: J. Immunol. **5**:239, 1920.
Stoland, D. D., and Sherwood, N. P.: J. Immunol. **8**:91, 1923.
Wedgewood, P. E.: M. Bull. Univ. Cincinnati, 1924, p. 178.
Wedgewood, P. E., and Grant, A. H.: M. Bull. Univ. Cincinnati, 1924, p. 172.
Weil, R., and Coca, A. F.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **17**: 141, 1913.
Wells, H. G., and Osborne, T. B.: J. Infect. Dis. **12**:341, 1913.
Zolog, M.: Compt. rend. Soc. de biol. **91**:215, 1924.
Zunz, E., and Gertruyden-Bernard: Compt. rend. Soc. de biol. **84**:287, 1921.
Zunz, E., and La Barre, J.: Compt. rend. Soc. de biol. **88**:654, 1923; **91**:132, 1924.

RACIAL VARIATION IN SIZE OF SPLEEN

A COMPARISON *

V. H. MOON, M.D.
PHILADELPHIA

For a number of years I have noted that the spleens of negroes as seen at autopsy are much below the average size of those of the white race. I have failed to find that such racial variation has been noted previously. If such observations have been made, the results do not show in the current literature on anatomy or pathology.

In the Philadelphia General Hospital, records of postmortem examinations, covering many years, are sufficiently complete to furnish suitable material. Accordingly, the data contained in those records were made the basis of this study. It cannot be claimed that these are normal spleens, since practically all of the subjects died as a direct result of disease. However, a consistent effort was made to exclude those cases in which marked pathologic enlargement of the spleen was probable. All cases in which the record showed splenomegaly, malaria, typhoid, acute splenic tumor, acute splenitis or leukemia were excluded. Also all cases in which the splenic weight was 350 Gm. or more were arbitrarily excluded as pathologically enlarged. A few small spleens, as described later, were omitted from the series. Only adults, i. e., those above 18 years of age, were studied. In this manner 1,000 cases among the negro race and 1,000 cases among the white race occurring during the same period were collected. The cases were taken consecutively, and the only selection was that already mentioned.

The 2,000 cases, divided as to race, sex and age, with the average weight of the spleen in grams and the ratio of the spleen to body weight for each group, are tabulated in table 1.

Table 1 shows the average weight of 1,000 spleens in adult negroes to be 106.25 Gm. as against 144.74 Gm. average weight of 1,000 spleens in white subjects. The average weight of negroes' spleens in the entire series is 73.5 per cent of the average weight in the white group. The spleen of the average white person weighs 136.2 per cent of that of the average negro. This difference of total average splenic weight, while marked, is much less than that actually present in corresponding age periods. It will be seen that in the negro group the total number of subjects, male and female, below 50 years of age is 616 as against 254 white subjects below 50 years of age. Since the spleen is largest in early decades and loses size markedly in the later decades, it is seen

* From the Department of Pathology, Jefferson Medical College, and Pathological Laboratories, Philadelphia General Hospital.

TABLE 1.—*Splenic Weight by Decades in the Negro and White Races*

Age	Male			Female		
	Cases	Spleen	Ratio	Cases	Spleen	Ratio
NEGRO						
18 to 29	85	120.1	1:375	140	112.6	1:337
30 to 39	98	119.6	1:410	96	107.2	1:432
40 to 49	106	119.9	1:457	91	101.6	1:485
50 to 59	80	110.4	1:480	86	97.1	1:546
60 to 69	70	100.6	1:545	65	80.9	1:544
70 to 79	38	88.2	1:724	26	67.9	1:612
80 to 89	7	80.7	1:740	8	85.6	1:580
90	1	60.0	1:660	3	41.7	1:964
All ages	485	112.3	1:472	515	100.5	1:460
Average weight of spleen, 1,000 cases: 106.25 Gm.						
WHITE						
18 to 29	39	171.5	1:300	18	168.0	1:238
30 to 39	48	166.7	1:298	32	145.7	1:305
40 to 49	94	161.9	1:304	42	146.0	1:322
50 to 59	135	146.4	1:324	77	135.3	1:352
60 to 69	176	153.3	1:370	108	139.2	1:334
70 to 79	108	146.4	1:355	79	108.3	1:420
80 to 89	33	146.5	1:348	25	88.0	1:464
90	3	116.6	1:418	2	112.5	1:466
All ages	617	152.9	1:327	383	131.5	1:338
Average weight of spleen, 1,000 cases: 144.74 Gm.						

TABLE 2.—*Splenic Weight in Corresponding Age Periods*

	Age	Cases	Total Splenic Weight, Gm.	Average Weight, Gm.
Negro	18 to 49	616	70,042	112.0
White	18 to 49	254	42,643	167.9
Negro	50 to 95	384	36,315	94.5
White	50 to 95	746	103,384	138.5

TABLE 3.—*Cases with Splenic Weight of 30 Gm. or Less*

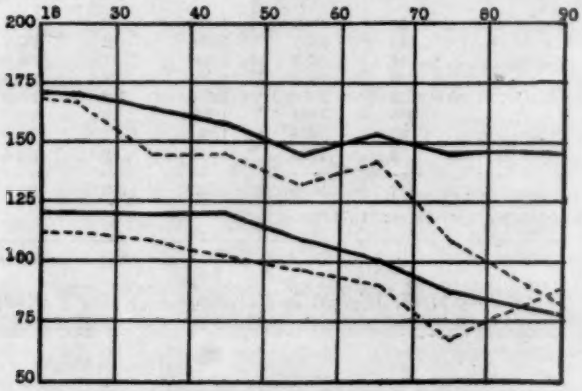
Race	Sex	Age	Cause of Death	Weight, Gm.
Negro	♀	49	Chronic ulcerative proctitis	30
Negro	♀	42	Cerebrospinal syphilis	30
Negro	♂	46	Pulmonary tuberculosis	30
Negro	♀	80	Arteriosclerosis	20
Negro	♀	44	Acute peritonitis	20
Negro	♀	49	Abscess, bronchopneumonia	15
Negro	♀	80	Arteriosclerosis	10
Negro	♂	29	Pulmonary tuberculosis	5
White	♀	72	Cerebral thrombosis	30
White	♂	91	Cardiovascular renal	30
White	♂	75	Senile dementia	25

that a majority of negro cases are from the period of life in which the spleen is large while the majority (746) of white cases are in the later period of life in which the spleen is smaller. Corresponding periods of life are compared in table 2.

In the period from 18 to 49 the average weight of the negro's spleen is 66.6 per cent of that of a white person. Correspondingly, the average weight of the spleen of a white person under 50 years of age is 150 per cent of that of the negro.

In the period of life above 50 years of age the average weight of the negro's spleen is 68.2 per cent of that of a white person; the average weight of the latter is 146.5 per cent of that of a negro.

The ratio of the weight of the spleen to the body weight for the respective groups is shown only for purposes of comparison. It must



Splenic weights of various groups. The upper solid line represents the average splenic weight of white males; the upper broken line, of white females; the lower solid line, of negro males, and the lower broken line, of negro females.

not be assumed that these represent even an approximation of the ratios existing in healthy normal adults. The bodies of a majority of these subjects were markedly emaciated, presenting a much wider deviation from normal body weight than was presented by the spleens of the same subjects.

In the chart the splenic weights for the various groups are shown graphically. The abscissae represent splenic weights in grams. Age is represented by the ordinates marking intervals of one decade.

The incidence of small spleens was greater in the negro than in the white race. Cases in which the spleen weighed 30 Gm. or less are enumerated in table 3 with the cause of death. None of these cases were included in the series of 2,000.

A racial comparison of the occurrence of spleens between specified weights is made in table 4.

A careful study of the clinical conditions and their relation to splenic size was not undertaken. Those cases which represented certain clinical conditions of common occurrence were grouped together, and the average size of spleen was computed for each group.

COMMENT

It is noted that acute infections have not caused as great average enlargement of the spleen in this series as would be expected. It must be borne in mind that many large spleens in this clinical group were excluded because of an anatomic diagnosis of acute splenitis or splenic

TABLE 4.—*Racial Comparison of the Occurrence of Spleens Between Specified Weight Limits*

Weight, Gm.	White	Negro
30 to 50	6	27
50 to 75	123	201
75 to 100	95	188
100 to 125	221	276
125 to 150	89	123
150 to 175	174	121
175 to 200	90	28
200 to 225	80	23
225 to 250	35	7
250 to 275	40	3
275 to 300	13	2
300 to 325	16	1
325 to 350	9	0

TABLE 5.—*Splenic Weights in Groups of Clinical Conditions*

	White		Negro	
	Cases	Average Spleen, Gm.	Cases	Average Spleen, Gm.
Acute infections	180	153.0	197	110.7
Tuberculosis	122	159.7	315	112.3
Syphilis	22	162.5	91	107.8
Carcinoma	212	133.2	94	92.6
Cardiovasculo-renal	290	129.5	220	90.8

tumor. The moderate enlargement found in tuberculosis and syphilis would be expected.

The fact that negroes tend to have much smaller spleens than white persons should be remembered when observations are being made on the size of the spleen in negro subjects.

A painstaking histologic comparison was not made in these cases. Such casual observations as were made did not show noteworthy histologic racial differences.

CONCLUSION

The average adult size of the spleen in the negro race is much below that of the white race.

The incidence of small spleens is greater and of large spleens is less in the negro than in the white race.

Laboratory Methods and Technical Notes

THE GRAM STAIN

II. Resistance of the Tuberculosis Leprosy Group of Organisms to Decolorization with Sodium Thiosulphate *

R. D. LILLIE, M.D.
Passed Assistant Surgeon, United States Public Health Service
WASHINGTON, D. C.

When a section known to contain large numbers of gram-positive organisms failed for some unknown reason to show these organisms after having been accidentally left for thirty or forty minutes in 1 per cent sodium thiosulphate, I was led to try out the effects of sodium thiosulphate on the Gram stain.

I was unable to find any reference to the decolorization of gram-positive organisms by thiosulphates in the literature.

EXPERIMENTAL PROCEDURE

EXPERIMENT 1.—Smears were made of a twenty-four hour culture of a fully gram-positive staphylococcus, air dried and fixed by heat. Staining was done as follows:[1]

Ammonium oxalate crystal violet	30 seconds
Wash in water	
Lugol's solution (I: 1, KI:2, H_2O: 100)	30 seconds
Wash in water	
Acetone to decolorize	5-15 seconds
Wash in water	
0.5 per cent safranine	30 seconds
Wash in water and dry	

Smear 1 was treated for ten minutes with 1 per cent sodium thiosulphate in 50 per cent alcohol, washed and stained by the foregoing technic with the following result: cocci all blue black.

Smear 2 was carried through the staining procedure to the point of the washing following decolorizing with acetone, treated two minutes with 1 per cent sodium thiosulphate in 50 per cent alcohol, washed and counterstained with safranine according to the foregoing technic with the following result: cocci all red.

Smear 3 (control) was stained according to the foregoing technic with the following result: cocci all blue black.

EXPERIMENT 2.—Smears of a mixed suspension of a fully gram-positive staphylococcus and a gram-negative bacillus (twenty-four hour cultures of each)

---

* From the Hygienic Laboratory.

1. Lillie, R. D.: The Gram Stain: I. A Quick Method for Staining Gram-Positive Organisms in the Tissues, Arch. Path. **5**:828 (May) 1928.

were air dried, heat fixed and treated as follows. Washing with water is to be understood after each step indicated. The crystal violet used was the same as that used in experiment 1. The iodine and safranine were also the same:

Smear 1 (control)			
Crystal violet	30 seconds		
Iodine	30 seconds		
Acetone to decolorize		Result:	Blue black cocci;
Safranine	30 seconds		red bacilli
Smear 2			
Crystal violet	30 seconds		
2 per cent sodium thiosulphate	90 seconds		
Iodine	30 seconds	Result:	Blue black cocci;
Acetone to decolorize			red bacilli
Safranine	30 seconds		
Smear 3			
Crystal violet, 2 per cent sodium thiosulphate Mixed	60 seconds	Result:	Blue black cocci;
Iodine	30 seconds		red bacilli
Acetone to decolorize			
Safranine	30 seconds		
Smear 4			
Crystal violet	30 seconds		
2 per cent sodium thiosulphate	90 seconds	Result:	Brownish black cocci;
Iodine	30 seconds		brownish black bacilli
Safranine	30 seconds		

EXPERIMENT 3.—Smears of two staphylococci (an albus and an aureus), a gram-positive diphtheroid and a gram-negative bacillus were made, air dried and heat fixed. The smears were then treated as indicated in table 1.

TABLE 1.—*Results Obtained with Smears of Staphylococcus albus and Staphylococcus aureus*

Procedure	S. Aureus	S. Albus	Diphtheroid	Gram-Negative Bacillus
Crystal violet .....30 seconds Iodine .....30 seconds Acetone q. s. Safranine .....30 seconds	Blue black	Blue black	Blue black	Red
Crystal violet .....30 seconds Iodine .....30 seconds Acetone q. s. 2 per cent sodium thiosulphate.60 seconds Safranine .....30 seconds	Red	Red	Red	Red
Crystal violet .....30 seconds Iodine .....30 seconds 2 per cent sodium thiosulphate.60 seconds Safranine .....30 seconds	Red	Red	Red	Red
Crystal violet .....30 seconds 2 per cent sodium thiosulphate.12 minutes	Violet	Violet	Violet	Violet

The first three experiments show that when 1 or 2 per cent sodium thiosulphate is applied to smears of gram-positive or gram-negative organisms at any point in the process of Gram staining before the application of iodine, Gram staining is not interfered with. When thiosulphate

solution is applied after the iodine, both gram-positive and gram-negative organisms are decolorized.

To determine whether this rule applied also to the acid-fast organisms, sections containing numerous tubercle bacilli were stained for sixty seconds with crystal violet and for thirty seconds in iodine, decolorized with acetone and then treated with 2 per cent sodium thiosulphate. After ninety seconds, the tubercle bacilli were still well stained, but they were decolorized after five minutes. They were counterstained with safranine according to the technic described in my first paper on the Gram stain.[1]

EXPERIMENT 4.—In order further to test the application of this reaction, smears were made of four to six weeks old cultures of all the available acid-fast organisms and of twenty-four hour cultures of twenty-two gram-positive organisms. The smears were air dried and heat fixed. One smear of each organism was gram stained, acetone being used as a differentiating reagent (reference should be made to experiment 1). One smear of each organism of the acid-fast group was stained by the Ziehl Neelsen method. One smear of each organism was treated as follows:

	For acid-fast group	For nonacid-fast group
Crystal violet	60 seconds	30 seconds
Iodine	30 seconds	30 seconds
Acetone	To decolorize	To decolorize
2 per cent sodium thiosulphate	90 seconds	30 seconds
Safranine	30 seconds	30 seconds

An additional smear of each organism of the acid-fast group was stained according to the foregoing technic with a variable length of application of the thiosulphate.

The results of these stains are summarized in table 2, except as to the variable exposure to thiosulphate, which I will discuss later. In general it may be seen that the ordinary gram-positive organisms are all decolorized by thirty seconds' exposure to the thiosulphate, with the exception of the two *Monilia* cultures, which showed incomplete removal of the Gram stain. This is probably accounted for on the basis of the large size of these yeasts relative to that of ordinary bacteria.

In general the acid-fast group shows a higher proportion of positive organisms by the thiosulphate procedure than by the Ziehl Neelsen method, and a still higher proportion by the Gram method.

Longer treatment (three minutes) with thiosulphate gave distinctly lower proportions of positive organisms than the ninety-second treatment, while shorter treatment of those smears showing smaller proportions of positive organisms gave a distinctly higher percentage of positive organisms.

The tubercle bacilli were still considered as fully positive after three minutes' treatment, but they showed distinctly less blue black and more pale violet forms, with or without deep blue beading (B C G, bovine 444 and 523, H37, avian, frog, turtle bacilli).

Two of these cultures, *B. leprae* 362 and *B. tuberculosis* 523 (bovine), were selected for more exhaustive tests. Six smears of each were made, one of each

TABLE 2.—*Results of Staining Bacterial Smears by Gram, Gram Thiosulphate and Ziehl Neelsen Methods*

Organism	Gram	Gram Thiosulphate	Ziehl Neelsen	Organism	Gram	Gram Thiosulphate
B. leprae, 361 (human)	+	+	+ (50% —)	B. tetani, Tulloch No. 2	+ (10% +)	— (few spores +)
B. leprae, 362 (human)	+ (few —)	± (5% +)	∓ (occasional +)	B. tetani, Tulloch No. 5	∓ (few +)	—
B. leprae, 364 (human)	+ (10-15% —)	+ (about 30% +)	+ (10-15% +)	B. anthracis, isolated 8-8-19	+ (few —)	— (occasional spore +)
B. leprae, 365 (human)	+ (few —)	+ (50% +)	+ (about 20% +)	B. anthracis, avirulent	+ (few —)	—
B. leprae, 330 (rat)	+	+ (few —, many pale)	∓ (rare +)	B. anthracis, Lloyd	+ (occasional —)	—
B. leprae, 368 (rat)	+ (occasional —)	+ (90% pale)	+ (50% +)	B. anthracis, Seattle, 1922	+ (few —)	—
B. leprae, 370 (human)	+ (few —)	+ (few —)	+ (20-30% +)	B. subtilis	+ (10-20% —)	— (occasional spore +)
B. leprae, 430 (human)	+ (few —)	± (about 10% +)	∓ (3-5% +)	Monilia psilosis, isolated 1-8-18	+ (50% +, few mixed)	∓ (few +) (few part +)
B. tuberculosis, No. 500 (B C G)	+	+	+ (50-60% +)	Monilia psilosis, No. 95, Porto Rico	+ (40% +, few mixed)	∓ (few partly +)
B. tuberculosis, No. 523 (bovine)	+	+	+	M. tetragenus	+	—
B. tuberculosis, No. 444 (bovine)	+	+ (few —)	+ (10% —)	Staphylococcus aureus, Pasteur Institute	+	—
B. tuberculosis, H 37 (human)	+	+ (few —, many pale)	+ (10% —)	Streptococcus scarlatinae, Dick, No. 2	+ (20-30% +)	—
B. tuberculosis, ranae	+ (15-20% —)	+ (few —)	∓ (occasional +)	S. viridans	+	—
B. tuberculosis, chelonis (Friedmann)	+ (many —)	+ (few —, many pale)	∓ (few +)	S. hemolyticus	∓ (few +)	—
B. tuberculosis, avian	+	+	+ (5% —)	Pneumococcus	+ (20% —)	—
B. smegmatis	+	+ (many pale)	∓ (few +)	B. acidophilus	+ (50-60% +)	—
B. stercussis (mist)	+ (some —, some ±)	+ (some —)	∓ (few +)	Staphylococcus (milk)	+ (20% —)	—
B. phlei (timothy)	+	+ (60-70% +)	± (5-10% +)			
B. diphtheriae, Park No. 8	+	—				
B. diphtheriae, isolated 4-11-24	+	—				
B. chauvei, Hopkins	+ (few —)	— (few spores +)				
B. chauvei, McFarland	+ (10% +)	— (few spores +)				
B. tetani, Tulloch No. 1	+ (10% +)	— (few spores +)				

was stained by the Ziehl Neelsen technic, and the rest were stained with crystal violet on the 50 C. hot plate for ninety seconds and washed. Of these last, one was carried through the remainder of my usual Gram technic (experiment 1). Two more were treated with Weigert's iodine for thirty seconds, and decolorized for from ten to fifteen seconds with acetone and then flooded with 2 per cent sodium thiosulphate, one being left for ninety seconds, the other for seventy minutes. A fourth smear was treated with iodine, and then with thiosulphate for seventy minutes; the last was treated with thiosulphate only for seventy minutes. After the thiosulphate was applied, all were washed and counterstained for thirty seconds with 0.5 per cent safranine, washed and dried.

The lepra bacillus culture was found not to be acid alcohol-fast, but was estimated as about 70 per cent acid fast to 5 per cent nitric acid; it was fully or nearly fully gram-positive, and about 70 per cent positive for the three treated with iodine followed by thiosulphate, with and without acetone, for ninety seconds, seventy minutes and seventy minutes, respectively. The crystal violet stain was not extracted by the thiosulphate when iodine was not used. The tubercle bacillus culture was fully positive throughout.

TABLE 3.—*Results of Sputum Staining by Ziehl Neelsen and Gram Thiosulphate Technics with Variable Lengths of Heating*

Time in Primary Stain	Number of Tubercle Bacilli Found by Ziehl-Neelsen Method	After Restaining by Ziehl-Neelsen Method	Number of Tubercle Bacilli Found by Gram Thiosulphate Method	After Restaining by Ziehl-Neelsen Method
15 seconds	Few, scattered	Numerous	Very occasional	Numerous
30 seconds	Few, scattered	Moderately numerous	Numerous	.....
60 seconds	Few, scattered	Numerous	Numerous	.....
90 seconds	Numerous	.....	Numerous	.....
2 minutes	Numerous	.....	Numerous	.....

From these experiments it may be concluded that the organisms of the acid-fast group differ from the gram-positive non-acid-fast bacteria in that, once having taken the Gram stain, they resist decolorization with sodium thiosulphate in a greater proportion than they do with acid alcohol and in some instances for over an hour, while the non-acid-fast group are decolorized in thirty seconds. On what chemical property of the acid-fast organisms this difference depends I am not prepared to state.

Spores also tend to resist decolorization with thiosulphate; these, in addition, as is well known, are often acid-fast.

In order further to test this differential staining of the acid-fast organisms sputum smears and sections of tuberculous and leprous material were also used.

A series of smears of a sputum known to contain tubercle bacillus were made, air dried, heat fixed and stained varying lengths of time on the 50 to 52 C. hot plate with Ziehl's carbol fuchsin and with ammonium oxalate crystal violet, respectively. The carbol fuchsin stains were decolorized for thirty seconds with 3 per cent anhydrous hydrochloric acid in 70 per cent alcohol, washed thoroughly, counterstained with 0.5 per cent methylene blue in 1:2,000 potassium hydroxide, washed and dried.

The crystal violet smears were washed, treated for thirty seconds with Lugol's solution (I: 1, KI: 2, H_2O: 100), washed, decolorized with pure acetone (about ten seconds), washed, treated for ninety seconds with 2 per cent sodium thiosulphate, washed, counterstained for thirty seconds with 0.5 per cent safranine, washed and dried.

After examination and recording of the results, all smears showing few or no tubercle bacilli were restained by five minutes' steaming in carbol fuchsin, and decolorized and counterstained as usual in order to control the results. As nearly as possible the same area was reexamined on each slide.

It would appear from table 3 that at least ninety seconds' heating at 50 C. was necessary to stain tubercle bacilli with carbol fuchsin, while thirty seconds' heating sufficed for the crystal violet.

In both this sputum and that from a patient with acute rhinitis, no other organism retained the violet stain when the Gram thiosulphate procedure was used, with ninety seconds' staining by the crystal violet at 50 C. Cold staining for the same time failed to stain the tubercle bacilli.

A series of sections of leprous tissue were stained, one section each, by the following technics: Ziehl Neelsen; Gram,[1] one minute cold, and ninety seconds at 50 C., respectively, in crystal violet; Gram thiosulphate, one minute cold, and ninety seconds at 50 C., respectively, in crystal violet; hematoxylin-eosin, and iron hematoxylin-van Gieson. This material comprised four spleens, three livers, two testes and seven skin nodules which were furnished me by Acting Assistant Surgeon O. E. Denny, in charge of U. S. Marine Hospital at Carvile, La. (National Leprosarium).

SUMMARY

The cold staining with the crystal violet failed to show more than a few bacilli either by the Gram method or by the Gram thiosulphate procedure. When heat was used in the crystal violet step, lepra bacilli were successfully stained. My impression is that the greatest number were shown by the Gram technic, the next greatest by the Gram thiosulphate method and the fewest by the Ziehl Neelsen method. Numerous bacilli were found in the liver and spleen blocks by all three methods, moderate numbers in the testes and few in the skin nodules.

The Ziehl Neelsen technic used consisted in heating the sections in a Coplin jar of carbol fuchsin for from forty to sixty minutes in the paraffin oven at 57 to 59 C., decolorizing them with 3 per cent hydrochloric acid in 70 per cent alcohol, and counterstaining them with methylene blue. The acetone xylene sequence was used for dehydrating and clearing.

As a further control, sections of experimental anthrax tissues were stained by Gram and Gram thiosulphate technics, the crystal violet being heated for ninety seconds at 50 to 52 C., and the thiosulphate being allowed to act only one minute. The anthrax bacilli were stained typically blue black by the Gram technic and all red by the Gram thiosulphate procedure.

Sections of an acutely inflamed appendix showing myriads of gram-positive streptococci and staphylococci in the fibrinopurulent exudate showed only red stained cocci after one minute's treatment with 2 per cent sodium thiosulphate.

CONCLUSIONS

1. When stained by the Gram method, the tuberculosis-lepra group of organisms resist decolorization with sodium thiosulphate longer than do other gram-positive organisms. 2. Nonacid-fast organisms when stained by the Gram technic are promptly decolorized by sodium thiosulphate. 3. This differential characteristic applies in sputum and in tissues as well as to smears of cultures. 4. Apparently, a larger proportion of the tubercle or lepra bacilli present in sputum or tissues may be demonstrated by means of this thiosulphate resistance technic than by the Ziehl Neelsen procedure.

CHEMICAL REACTION OF PHYSIOLOGIC SODIUM CHLORIDE USED IN THE KAHN TEST*

XAVIER HERNANDEZ, M.D., MEXICO CITY, MEXICO

The results of the Bordet-Wassermann reaction are known to be markedly affected by traces of acid or alkali in the reagents.[1] It seemed important to determine whether and to what extent this may be true in the case of the Kahn reaction. The results of a study of the effect of the addition of acid and alkali to the serum and antigen used in this reaction have already been reported by Kahn.[2] The question arose as to whether it was essential that the physiologic sodium chloride which is used in this reaction be neutral and to what extent departures from neutrality would affect the accuracy of the results.

Physiologic sodium chloride even if neutral on preparation does not remain so. Exposure to the air soon renders it acid due to the absorption of carbon dioxide. Then again when pipets are emptied, the last drop is generally "blown out," which brings about the addition of still more carbon dioxide. Furthermore, workers do not always use the utmost precautions in employing neutral glassware in the preparation of salt solution.

EXPERIMENTAL WORK

Two series of experiments were performed. In one series, the effect on the Kahn reaction of varying the H-ion concentration of the salt solutions was studied, and in the other series, the effect of adding relatively excessive amounts of acid and alkali was noted. In series 1 the acidity or alkalinity is expressed in terms of the p_H value of the solution, whereas the normality of the solution with respect to the added acid or alkali is used to describe the more concentrated solutions occurring in series 2.

SERIES 1.—Fifteen hundred cubic centimeters of physiologic sodium chloride was prepared by dissolving 12.75 Gm. of chemically pure sodium chloride in redistilled water. This was divided into three parts. Part 1 was brought to a p_H of 6, part 2, to one of 7, and part 3 to one of 8. For the p_H determina-

---

*From the Bureau of Laboratories, Michigan Department of Health, Lansing, and the National Department of Public Health, Mexico City.

1. Brown, C. P., and Kolmer, J. A.: Am. J. Syph. **3**:1, 1919.

2. Kahn, R. L.: Serum Diagnosis of Syphilis by Precipitation, Baltimore, Williams & Wilkins Company, 1925.

tions, the calorimetric method of Barnet and Chapman was employed. These three salt solutions were used in performing three series of Kahn tests on the same groups of serums, standard antigen being used throughout. Any variations in the results of the three series would thus necessarily be due to the salt solution. The three series of tests were made with ten serums a day until a total of fifty serums had been employed with each of the prepared salt solutions. The results are summarized in table 1. The regular three-tube Kahn test was employed in each case, but in order to save space, the results in the table represent the average of the observations in the three tubes. It is evident that the Kahn reaction is practically unaffected by variations of from 6 to 8 in the p_H value of the salt solutions.

TABLE 1.—*Kahn Reactions with Salt Solutions of Varying p_H*

Serum No.	p_H 6	p_H 7	p_H 8
1 to 18	++++*	++++	++++
19 to 20	+++	+++	+++
21	+++	+++	++++
22	+++	++++	++++
23	++	++	++
24	++	+++	+++
25 to 26	+	+	+
27 to 30	±	±	±
31	±	±	+
32 to 50	0	0	0

* The results represent the average of the observations in the regular three-tube Kahn test.

TABLE 2.—*Kahn Reactions with Salt Solutions of Varying Acidity*

Serum No.	Control Salt Solution p_H 7	0.01 N	0.02 N	0.03 N	0.04 N	0.06 N	0.08 N
1 to 5	++++	++++	++++	++++	++++	++++	++++
6 to 7	+++	+++	++++	++++	++++	++++	++++
8	++	+++	+++	+++	+++	+++	++++
9 to 10	++	++	++	++	+++	+++	+++
11	±	±	±	+	+++	+++	+++
12	±	±	++	++	++	++	+++
13 to 14	0	0	0	++	+++	+++	++++
15 to 16	0	0	0	±	±	+++	++++
17 to 18	0	0	0	±	±	++	+++
19	0	0	0	0	+	++	++
20 to 23	0	0	0	0	±	++	++
24 to 26	0	0	0	0	0	+	++
27 to 31	0	0	0	0	0	±	±
32 to 35	0	0	0	0	0	0	0

This experiment was repeated with salt solutions of p_H 5, 7 and 9, these three salt solutions being similarly employed in triplicate Kahn tests with fifty different serums as in the experiment already mentioned. In this case also significant variations in the reactions were not observed.

Finally, salt solutions were prepared of p_H 4, 7 and 10 and again employed in triplicate Kahn reactions with fifty different serums. Again the variations in the results were not greater than those listed in table 1. It seemed, therefore, that changes in the p_H of physiologic sodium chloride extending from 4 to 10 have practically no effect on the accuracy of the Kahn reaction.

SERIES 2.—In this series, varying amounts of normal hydrochloric acid and sodium hydroxide were added to the physiologic sodium chloride that was

subsequently employed in the Kahn reaction. Salt solutions were prepared with the following six acid concentrations: 0.01, 0.02, 0.03, 0.04, 0.06 and 0.08 normal hydrochloric acid. These acidified salt solutions were used in the Kahn reactions with different serums; a salt solution of p_H 7 was used as a control. In order to employ all these salt solutions at one time, it was necessary to limit the experiment to a one-tube Kahn test. The "middle" tube was chosen in which 0.025 cc. antigen suspension was used with 0.15 cc. serum. All other steps were carried out in the same manner as in the regular three-tube Kahn test. Table 2 gives the results of this experiment. It is seen that 0.01 and 0.02 normal acid concentration in the physiologic sodium chloride have apparently no effect on the accuracy of the Kahn reaction. Beginning with 0.03 normal acid concentration, however, nonsyphilitic serums begin to show weak precipitation reactions. These reactions are increased in intensity with the increase in acid concentration of the salt solution.

In a similar experiment, alkali instead of acid was added to the physiologic sodium chloride, concentrations of 0.01, 0.02, 0.03, 0.04, 0.06 and 0.08 normal

TABLE 3.—*Kahn Reactions with Salt Solutions of Varying Alkalinity*

Serum No.	Control Salt Solution p_H 7	0.01 N	0.02 N	0.03 N	0.04 N	0.06 N	0.08 N
1	++++	++++	++++	++++	++++	++++	++++*
2	++++	++++	++++	++++	++++	++++	++
3	++++	++++	++++	+++	+++	+++	++
4	++++	++++	++++	+++	+++	++	++
5	++++	++++	++	++	+	+	+
6 to 7	++++	++++	+	±	0	0	0
8 to 9	++++	++	+	0	0	0	0
10 to 13	+++	+	0	0	0	0	0
14 to 15	++	+	0	0	0	0	0
16 to 18	+	0	0	0	0	0	0
19 to 20	±	0	0	0	0	0	0
21 to 35	0	0	0	0	0	0	0

* This serum continued to give ++++ reactions even when normal sodium hydroxide was substituted for physiologic sodium chloride in the Kahn test.

sodium hydroxide being employed. Table 3 summarizes the results obtained with thirty-five serums. A tendency for reduction in sensitiveness of precipitation reactions is noted beginning with 0.01 normal alkali. This tendency increases with the increase in the alkali content of the salt solution. It is of interest to note that one strongly positive serum persisted in giving strong precipitation reactions even when normal sodium hydroxide was substituted for physiologic sodium chloride in the Kahn test.

Kahn has already shown that excessive amounts of acid (about 0.03 normal hydrochloric acid) in nonsyphilitic serum will produce strong precipitation reactions, and that excessive amounts of alkali (about 0.01 normal sodium hydroxide) in syphilitic serums will render them negative. The addition of similar amounts of acid or alkali to the physiologic sodium chloride used in the Kahn test apparently exerts the same effect.

SUMMARY

An attempt was made to determine whether differences in the H-ion concentration of the physiologic sodium chloride used in preparing the antigen suspension in the Kahn reaction have any effect on the accuracy of this reaction. It was found that salt solutions of p_H 6, 5 and 4 as well as 8, 9 and 10 give results closely parallel to those obtained with salt solution of p_H 7.

It was then attempted to find whether salt solutions containing as much as 0.01 normal acid or alkali or more concentrated solutions will still not affect the accuracy of the Kahn reactions. The results indicate that salt solutions containing 0.01 or 0.02 normal hydrochloric acid have practically no effect, while 0.03 normal hydrochloric acid begins to give weak, falsely-positive reactions. These reactions become more intense with the increase of acid. When sodium hydroxide was added to physiologic sodium chloride, it was found that 0.01 normal sodium hydroxide was sufficient to weaken positive Kahn reactions. When the concentration of alkali was increased to 0.02 and 0.03 normal, some four plus reactions were reduced to practically negative reactions.

It appears from these results that the accuracy of Kahn reactions is not affected by slight changes in the H-ion concentration of the salt solution used in this test, but is affected when the salt solution contains as much as 0.03 normal hydrochloric acid or 0.01 normal sodium hydroxide.

General Review

ECTOPIC ENDOMETRIOSIS*

VICTOR C. JACOBSEN, M.D.
ALBANY, N. Y.

The endometrium is a tissue which, in some degree at least, is subject to many hormonal stimuli. At puberty it begins to respond to the ovarian influence, and until the climacteric intervenes it will, in the absence of pregnancy or other disturbing factors, undergo engorgement about every twenty-eight days, swelling and breaking down with hemorrhage, followed by rapid and complete repair—the phenomenon of menstruation. During pregnancy other changes, together with decidual stromal metamorphosis, further complicate and add to the many structural mutations which are the normal lot of this remarkable tissue.

If one considers the host of disturbing factors in the physiology of the female, it is not surprising that the endometrium manifests a varied group of pathologic conditions which may be largely the result of endocrine dysfunction or imbalance. The necessity for replacement of much tissue lost during the menses often leads to excessive reproduction of endometrium, and the hypertrophied membrane in turn is more susceptible to ovarian and other endocrine influences than is the normal tissue. Hence, a study of the normal physiology of the generative tract of the female should lead one to expect many pathologic states based in greater or less degree on the frequent alterations it undergoes.

It is within the short period of the past six years that a new and yet fundamental aspect of the pathologic processes in the female has claimed the attention of physicians. It concerns heterotopic or ectopic endometrium-like tissue or, to use another term, ectopic endometriosis, a condition in which tissue of endometrial appearance and function is found in divers places outside the uterine cavity. This subject cannot be reviewed in its proper perspective, however, without a preliminary survey of the literature on adenomyoma, which has a much older history and which embraces the earliest recorded, if not understood examples of misplaced endometrium.

The name of von Recklinghausen must always be associated with the earliest attempts at understanding the adenomyoma. In 1895, he published his famous wolffian theory, in which he endeavored to explain the diffuse uterine adenomyoma and that arising in the cornual end of the fallopian tube on the basis of congenital rests from the wolffian

* From the Albany Medical College.

anlage. While his theory has few if any supporters today, it was the first major contribution toward the elucidation of these growths and focused attention on them. The adenomyoma of the interstitial portion of the fallopian tube has been studied by Chiari, Martin, Orthmann, Werth and Shauta, and the names given it indicate the understanding of the condition of the various observers. Adeno-myo-salpingitis, adenomyositis tubae and salpingitis isthmica nodosa, all these terms convey the idea of a basic inflammatory process.

The subserosal adenomyoma of the uterus was regarded by Iwanoff, in 1898, as arising from a transformation of peritoneum into the gland structures present in the tumor. He was supported in this contention by Aschoff, Pick and Robert Meyer. This theory is in direct conflict with Cullen's explanation of the uterine adenomyoma, a diffuse type of which, in 1896, he proved conclusively arose by direct invasion from the mucosa. In 1887, Chiari described a nodular swelling of the fallopian tubes which he called salpingitis isthmica nodosa, a condition now known as adenomyoma of the tube. He found that the mucosa of the tube sent prolongations into the wall, some being cut off from the lining to form cysts. This observation of Chiari's was an important contribution to the explanation of the adenomyoma due to direct invasion of the muscle wall by endometrial glands and stroma, and it formed the basis for Cullen's subsequent extensive studies on uterine adenomyomas.

In 1918, Lockyer published his "Fibroids and Allied Tumours" and reviewed the literature of adenomyoma up to that year. In 1891, Baraban reported a uterine growth which he regarded as of mucosal origin. In 1894, Pilliet further suggested that the cysts and glands of adenomyoma were of mucosal origin. Lockyer collected and abstracted from the literature the reports of forty-seven cases of adenomyoma of the rectogenital space. The first case was that of Pfaenenstiel in 1897, who regarded it as of wolffian origin. The reports of only four cases were from this country, and all were contributed by Cullen.

The extra-uterine adenomyomas were little known during the twenty years following von Recklinghausen's publication, and the rectovaginal space was usually the site involved. Meyer has attributed the subserous and ectopic adenomyomas to a primary inflammation with peritoneal metaplasia into glands and secondary epithelial heterotopy or displacement. He has many followers, particularly on the continent, including Semmelink and Josselin de Jong. During the period of ascendancy of the serosal theory, Cullen remained steadfast to the view that the subperitoneal adenomyomas were of mucosal origin, and that the extra-uterine gland elements were derived from congenital müllerian rests.

In 1918, Ewing described adenomyomas in the broad and round ligaments, groin, cervix, vaginal wall, fallopian tubes and rectum. Mahle, in 1921, reported twenty-one cases of adenomyomas of the

fallopian tube. Herly stated that adenomyoma of the rectovaginal septum has been mistaken for hematocele, pelvic abscess, cancer of the rectum and adherent adnexa in the pouch of Douglas.

It may be well to observe that the term adenomyoma has been and still often is used incorrectly. Myoma is a tumor derived from muscle. An adenomyoma, then, should be a muscle tumor containing glands. In the case of the uterine adenomyoma, the glands are almost invariably accompanied by normal appearing endometrial stroma which has a distinctive appearance. While simple heterotopy of endometrial glands and stroma causes a diffuse enlargement of the uterus, it does not constitute an adenomyoma, although the term is not infrequently used in that way. A true myomatous reaction about heterotopic endometrial glands and stroma does occur, however, not only within the uterine wall but also in more remote situations, in the rectovaginal margins and in the wall of the intestine. Since glands and stroma constitute the endometrium, the term endometrioma of Bell is a more accurate descriptive name, although adenomyoma has almost acquired respectability through the sanction of long use. I do not believe that the use of the suffix "oma," as indicative of true neoplasia, in the absence of myoma is justified.

The etiology of extra-uterine pelvic growths of adenomyomatous nature was not satisfactorily explained until the various types of hemorrhagic cysts of the ovary were finally classified correctly. In 1899, Russell published a report of a case in which uterine mucosa was found in an ovary. He regarded his observation as due to an anomalous point of development of portions of the müllerian duct in the germinal epithelium. Frederica Winestine states that von Franque (1898), Naumann (1898) Agnes von Babo (1900) and Vassmer (1901) had also seen the condition. Ludwig Pick, in 1905, reported five cases of endomentrial tissue in the ovary, which he called adenoma or cystoma endometrioides ovarii. Bilateral or unilateral cysts, lined by tissue identical with that of the interior of the uterus, were present in two cases. Genesis of the cysts was attributed to dilatation of the endometrial glands as a result of menstrual bleeding. Pick's first idea was that the endometrial tissue in the ovary was derived from wolffian rests, as von Recklinghausen had believed. Later he concluded that it arose from the superficial epithelium of the plica urogenitalis.

Lockyer, in his "Fibroids and Allied Tumours," describes a specimen of Semmelink and de Jong. The ovary was adherent to an adenomyomatous uterus. A blood cyst partly lined by adenomatous tissue was found in the ovary and similar tissue in spaces in the periphery of the ovary. In 1919, Casler reported a case in which the patient menstruated through the vagina after conservative hysterectomy in which one ovary was saved. The uterus was removed for an adenomyoma

which contained stroma but no glands. Four years later, the enlarged remaining ovary was removed and found to contain cavities lined by "normal uterine mucosa." In an article on the distribution of adenomyomas containing uterine mucosa, Cullen, in 1920, described three specimens of ovaries in which there was uterine mucosa. In one ovary a cyst was lined with a brownish membrane histologically resembling normal endometrium. Norris, in 1921, and Janney, in 1922, found menstruating endometrium in an ovary.

Runge and Wolf have demonstrated the epithelialization of ovarian hematomas by the invasion of the surface epithelium of the ovary through the opening caused by rupture. Wolf also believes that gland-like structures in the underlying stroma arise from a pushing downward of the overlying epithelium. These and similar observations bring forward the concept of metaplasia of peritoneal mesothelium into endometrial glands, and it is on this point that the two main schools of thought disagree. This will be discussed in more detail later.

The studies of Sampson relating to endometrial cysts of the ovary and to primary and secondary endometriosis will undoubtedly form a landmark in the literature of gynecologic pathology. For the past six years his views have been the stimulus for a vast list of publications from all parts of the world; hence his series of investigations will be reviewed in some detail.

In 1921, in his first paper on this subject, Sampson discussed the perforating hemorrhagic (chocolate) cysts of the ovary. These cysts are often bilateral and are usually small, from 2 to 4 cm. in diameter, although they are occasionally smaller than 2 cm. and larger than 4 cm. They develop in women during their menstrual life, especially from the thirtieth year to the menopause. Many of the cases reported by Hedley, Savage, Wolf and that of Smith probably belong to this group. At operation the ovary containing such a cyst is adherent because of a previous perforation and is ruptured in freeing it. The perforation is sealed by the structure to which the cyst at that site has become adherent, such as the posterior wall of the uterus, posterior layer of the broad ligament or peritoneum of the side of the pelvis. Histologically, the lining of the ovarian hematomas of this type is similar to that of the uterine hematomas due to retention of menstrual blood often present in adenomyoma of the uterus. Periodic (menstrual) hemorrhages occur in these endometrial lined cavities, and the contents become a chocolate color, resembling old menstrual blood.

When such a cyst of the ovary ruptures, soiling of pelvic tissues occurs, and in certain instances secondary implantations of functioning endometrial tissue develop on the ovary, uterus, tubes, in the culdesac or in the rectovaginal septum. Sampson concluded that the perforating endometrial cysts of the ovary with their secondary implants were as

definite a pathologic entity as they were a clinical entity, capable of diagnosis before operation in a large percentage of cases. As to the incidence of the condition, in one year he found fourteen cases in 178 patients between 30 and 50 years of age.

After a study of more material, Sampson, in 1922, was able to detect various stages in the development and retrogression of ectopic endometrial foci. He had observed forty cases of perforated ovarian hematomas of endometrial type and found pelvic implantations in all but one specimen. In three cases without perforation implants were not detected. In twelve cases, portions of the intestinal tract were involved in this type of growth. He reported a case in which he removed a large myomatous uterus containing an early pregnancy (accidental observation). A perforated ovarian hematoma of endometrial type was present in the left ovary. Decidual reaction was found in the lining of the hematoma and in the peritoneal adhesions.

In this same article he emphasized the idea that tubal and uterine epithelium would be more likely to escape from the fimbriated end of the tube during the menstrual life of the patient rather than before puberty or after the menopause. When the condition exists, the uterus is often retroflexed and contains myomas and polyps, conditions which might favor a backflow of menstrual blood. He states,

> I consider the ovary as a sort of intermediary host, hotbed or incubator which imparts greater virulence to the epithelial cells developing in it, but it may not be an essential intermediary host in the origin of implantation adenomas of endometrial type.

A more complete study of intestinal endometriosis was published by Sampson, in 1922, under the title "Intestinal Adenomas of Endometrial Type." At that time he commented on the increase in the number of cases of perforated endometrial cysts of the ovary in his own practice. He attributed this to his increasing ability to recognize the anatomic lesion. He reported twelve cases of intestinal endometrial implantation, of which eight involved the rectum, sigmoid, epiploic appendage or mesocolon, four the appendix and two the small intestine. The distribution of the ectopic endometrium was the same as that often seen of implants from an ovarian carcinoma. The intestinal endometrial implants, however, grew less rapidly, were not so invasive and their distribution not so wide as carcinoma.

In the intestine the type reaction to the presence of the endometrium was a fibrosis with adhesions, and at times a myomatous change in the muscle invaded. The intestinal lesions rarely gave rise to symptoms, but various degrees of intestinal obstruction were seen which necessitated radical surgery. Sampson regarded the epithelium escaping from an ovarian endometrial hematoma as probably the principal source of the

intestinal implantations. He mentioned the additional possibility that some of them may have arisen from tubal and uterine epithelium escaping through the fimbriated end of the tube, independently of an ovarian hematoma with perforation.

In the same year Sampson discussed the life history of ovarian hematomas of endometrial (müllerian) type. The preceding year he had found thirty-seven cases of ectopic endometriosis out of 170 women between 30 and 50 years of age on whom abdominal operations were performed for pelvic conditions. He emphasized the fact that implantations of epithelium escaping from the fimbriated end of the tube could take place on one or both ovaries, pelvic peritoneum or intestines. He attributed the partiality of endometrium for implantation in the pelvis to the habit of women spending the greater portion of the day with the body in the upright posture, whether sitting or standing, the "sediment" from the tube naturally settling on the lateral and under surface of the ovary and in the bottom of the culdesac. The hematoma would attain its greatest size in the ovary, reaching several centimeters in diameter. Those elsewhere tended to grow in tubules, rarely with small cyst formation. The ovary was regarded as unusually good soil for the growth of endometrium but not a necessary intermediate host.

In 1922, Jacobsen reported the successful autotransplantation of endometrium in the peritoneal cavity of the rabbit. He cut out a portion of one cornu, scraped off the mucosa and sowed the fragments in the abdominal cavity. After from 60 to 280 days, the animals were killed. When the animals were in heat at the time of operation, implants were obtained in about 83 per cent of animals, when in the resting stage in only about 16 per cent, indicating a greater virulence for endometrium in the state of "heat" or estrus. He amplified and confirmed this work, and later was able to produce implantation on the intestine and urinary bladder by the same technic. Most of the implants were found in the pelvis, but in contrast to the human lesions they were invariably cystic, often multilocular and greatly resembled the papillary cystadenoma of the ovary. There was also no hemorrhage into the cyst cavities. Monkeys (*Macacus rhesus*) were then used by Jacobsen for similar experimentation, since Corner had shown that menstruation may be regular in the monkey. Five animals were subjected to hysterotomy, the endometrium curetted out as thoroughly as possible and the curettings sowed in the peritoneal cavity. In one animal, implants were found on the serosa of the uterus after three weeks. After twelve months, the other four monkeys were killed. One did not show any implants. Three contained typical endometrial growths on the uterus and in the culdesac. One animal, which was menstruating at the time it was killed, showed typical menstrual hemorrhage into implants on

the serosa of the uterus. These experiments with monkeys are the closest approximation to the human condition yet attained.

Stilling, in 1909, had transplanted successfully fragments of uterus into the spleen of the rabbit, and Hesselberg, Kerwin and Loeb into the ear of the guinea-pig. Katz and Szenes, Blair Bell, Spirito, Dossena, Michon and others have confirmed Jacobsen's observations in the rabbit, guinea-pig and rat, their observations being supportive of Sampson's idea that on reaching the peritoneal cavity fragments of living endometrium may become implanted on various organs and grow. The ectopic endometrium in the experimental animal as in women is subject to the ovarian hormone, as was shown by Jacobsen and Katz and Szenes. These workers state:

> Our researches show, as in Jacobsen's experiments, the development of cysts from transplanted endometrium and further prove the absolute dependence of this growth on the ovary. In two cases where a time period from thirty-one to sixty-one days respectively had elapsed between castration and the implantation of endometrial tissue, no cyst formation took place. These experiments also give support to Sampson's conception of the origin of the "chocolate" cysts in women, although, of course, the information is yet to be brought forward as to the manner in which the vitality of the endometrial cells in the peritoneal cavity could be maintained. With the great number of observations by Sampson of the "chocolate" cysts and the frequent tubal insufflation by Rubin, it is interesting to speculate as to how many cases of Sampson's had had a previous insufflation of the tubes.

They quote Professor Peham as saying it is possible that tubal insufflation could give rise to chocolate colored cysts.

O'Keefe and Crossen transplanted endometrium in seven dogs, placing the tissue in definite locations, such as the ovary, meso-appendix, right rectus muscle, and in the fold between the appendix and cecum. They obtained "takes" in the meso-appendix and ovary.

In discussing a case of endometrial tissue in the abdominal scar following cesarean section, Schwartz mentions some experiments he had made on the cesarean scar of the guinea-pig. In several animals he found endometrial tissue along the incision as well as on the peritoneal surface of the uterus. He was impressed by the readiness with which endometrial tissue developed in these locations in the guinea-pig.

Michon transplanted minute pieces of endometrium into the ovary of the rabbit. He used four animals, and the tissue grew in each instance with the formation of cysts. He considers the ovary well adapted to this type of graft, and his experimental results offer a serious argument in favor of Sampson's implantation hypothesis. He regarded the growths he obtained in the ovary of the rabbit as really adenomyomas, since there was a hyperplasia of smooth muscle around the transplanted epithelium. It is possible, however, that he introduced

smooth muscle fibers along with uterine mucosa; hence the term adenomyoma may not be justified in this case.

The publication of Sampson's papers was followed by a large number of observations from many countries, some supporting, others criticizing his hypothesis, and still others unconvinced one way or the other. The theories presented in explanation of ectopic endometriosis soon were divisible into three main groups: (1) The serosal theory of Iwanoff, Meyer, Pick and others. The supporters of this idea believe that typical uterine mucosa can arise by a metaplasia of peritoneal mesothelium, with subsequent invasion of the underlying tissue and the acquiring of the menstrual function. (2) The metastatic theory of Halban, which implies a ready invasion of uterine lymphatics by endometrium which is thus transplanted to the ovary and all peritoneal sites. (3) The implantation theory of Sampson which has just been described.

Halban's theory of metastatic hystero-adenosis has found little acceptance and does not explain the majority of ectopic endometrial foci. Sampson, however, had called attention to the possibility of invasion of the lymph vessels by endometrium and suggested this route in cases of inguinal endometriosis. He mentioned also that endometrial-like glands had been seen by Dr. Fred J. Taussig of St. Louis and in a retroperitoneal lymph node sent to me by Dr. N. C. Foot of Cincinnati. Ries, Wertheim and Wulfing have reported similar observations.

The serosal theory still finds warm protagonists, particularly in Germany, less so in America. Lauche, in 1923, writing at length on extragenital heterotopic adenomyomas, emphasized their participation in menstruation and the fact that they occurred only in the female and during the sexual life. Lauche advanced the theory of peritoneal origin due to stimulation by the ovarian hormone. Later, however, he accepted Sampson's explanation for a few of his cases, and in some German circles the implantation hypothesis is referred to as the Sampson-Lauche theory.

Robert Meyer is the most ardent defender of the serosal theory and goes so far as to say that the celomic epithelium everywhere is of such quality as could produce endometrial tissue, in spite of the fact that endometriosis has never been found in pleural or pericardial cavities or very far outside the pelvic limits of the peritoneal cavity. Recently he stated that heteroplasia on the basis of congenital predisposition and dependent on ovarian activity or other stimulating influences is a sufficient explanation for endometrium being found in the tube, for instance, although the presence of menstruating tissue in the tube may or may not have a similar origin to other ectopic foci. Meyer takes a definite stand against Halban's theory of lymphatic metastasis. He lays much stress on his own observation that elastic tissue is not found in the uterine mucosa, but is present in ectopic endometrium-like

tissue, and that therefore the latter could not have originated from endometrium. Lochrane, however, found elastic fibers in normal uterine curettings.

The peritoneal mesothelium is usually described as a single layer of pavement cells which in profile appear as thin scales with projecting nuclei. When an irritant has been present, for instance about adhesions, the mesothelium is often low cuboidal. When a low grade inflammation is in progress, the lining cells often become columnar, and may even form what in a fixed preparation appear to be cilia. Whether these brushlike processes are true cilia has not been precisely determined. A zoologist would insist on seeing the processes actually move as cilia in a fresh preparation before he would accept them as being cilia. It might be allowed, however, that under certain conditions the mesothelium can become columnar and develop hairlike processes which closely resemble true cilia. In granting this, a point is gained for the serosal (Meyer) theory of ectopic endometriosis, since the tubes and parts of the uterus are lined by ciliated epithelium.

However, another and probably more important tissue must be present in a lesion before it can be identified as of endometrial type, namely, the so-called "cytogenous" stroma. This stroma is of a texture peculiar to endometrium and is seldom to be mistaken for that of any other organ. Many publications on this subject include illustrations showing various degrees of infolding of peritoneum with the production of glandlike spaces, some of which are lined by ciliated cells. There is also pictured true endometrium growing on and invading peritoneal surfaces, but so far as I can determine, the adherents of the serosal theory have yet to demonstrate endometrial stroma about the glandlike structures arising from infolding or downgrowth of mesothelium. It need not be necessary to show menstrual changes in every heterotopic endometrial growth, since they do not react equally in that respect, but it seems reasonable to insist on the presence of typical stroma in pronouncing any of these peritoneal metaplasias of endometrial type.

Another point of possible error in interpretation arises when a true endometrial ovarian cyst has eroded the germinal epithelium which has later grown into and partly "mesothelialized" the cyst. Some observers have regarded this as a transformation of germinal epithelium into endometrium. As Ewing has said, the metaplasias which the peritoneal mesothelium may undergo will offer many lesions difficult of classification. The fact that the celomic epithelium gives rise to müllerian tissues in the embryo makes it necessary to consider the possibility that it may form such tissues postnatally, even though such an idea is objectionable from a general biologic point of view. So far the theory has been staunchly defended and has stimulated a careful review

of the properties of mesothelium; all that is lacking is a demonstration that peritoneal cells can form endometrium in postpartum life.

The implantation theory of Sampson, although much discussed in Germany, has found few supporters there, gynecologic and other pathologists being influenced unfavorably by the dicta of Robert Meyer and his school. Vogt, however, tends to agree with Sampson. He states that tubal menstruation may be only the backflow from the uterus, and that some extra-uterine pregnancies may be explained by the ovum getting into an endometrium-like area in an ectopic focus. In 1923, Sutton described a primary ovarian pregnancy in which part of the gestation cavity in the ovary was lined by endometrium. Vogt also warned of dangers in the Rubin test, the uterine insufflation possibly forcing endometrial fragments into and through the tubes.

Stubler regarded the implantation theory as not probable because if true, pelvic implants should occur more often in carcinoma of the uterus. He believed that cancer metastasizes to the tubes through the lymphatics. He said that the theory that a backflow of blood from the uterus is due to retroflexion had not been proved. He stated categorically that endometrium cast off at menstruation is not viable, but he did not offer any proof for that assertion. He said that he did not accept Jacobsen's experiments because it is not reasonable to believe that endometrium can be transplanted if such sensitive tissue as that of the ovary cannot be transplanted with success. Stubler believes that the ectopic endometrium in the ovary arises from the germinal epithelium. He did not account for the blood, the pigment or the typical endometrial glands seen.

In 1924, Van Oettingen and Linden reported a series of twenty ovarian cysts containing endometrial tissue. They found deep and superficial types of ovarian endometriosis. The deep type was derived from ovarian epithelium which grew down and since it had connection with the surface of the ovary, Sampson's theory was wrong. The superficial type arose from rupture of a deep cyst and not from the uterus since the ostium of the tube is too small to permit passage of such bits of tissue. The escaping blood irritates the peritoneum which under ovarian influence develops into uterine mucosa. Secondary implantations, however, were possible. Women with this heterotopia were regarded as constitutionally inferior.

After studying ten cases of ectopic endometriosis, Semb concluded that the endometrial tissue in the ovary arises from follicular epithelium, or possibly is associated with epithelial defects in the ovary. To explain endometriosis in the serous layer of the uterus, small intestine and round ligament he tends to agree with de Jong that the different localizations can be traced to endometriogenic potentialities of the celomic epithelium. He did not find any evidence in support of the

theories generally advanced, in particular none in favor of Sampson's implantation theory, which is not considered to fit in with the endometrial "tar cysts."

Lahm, in discussing adenomyosis of the female genital organs, was of the opinion that inflammation was not necessary. In the lesions developed from müllerian ducts, their origin was due to spaces left in the laying down of the uterovaginal mesenchyme into which under definite stimuli the uterine or tubal mucosa grows. The stimulus is regarded as due to dysfunction of the ovary and is somewhat similar to the decidual reactions. Any inflammatory changes were always secondary.

The British gynecologists were early students of endometriosis and have contributed valuable observations both clinical and anatomic. Shortly after Sampson's first report, Blair Bell, in 1922, published a paper on endometrioma and endometriomyoma of the ovary. For many years, he had referred to adenomyoma of the rectovaginal septum, uterosacral and round and ovarian ligaments and fallopian tube as endometrioma and endometriomyoma. At that time he was doubtful whether the "cellular spill" from a ruptured ovarian cyst could result in implantations, but more recently he has admitted the possibility. He felt it probable that all unstriped muscle fibers in relation to endometrial tissue in the ovary are merely those which are normal in the ovary but which have undergone hyperplasia. The condition was caused by congenital aberration of müllerian tissue when not due to direct contact. He stated:

> It is not easy to understand how independent endometriomata of the umbilicus or ovaries arise, or rather, to visualize the developmental irregularity that leads to aberration of this tissue so far afield, without there being any trace of the path by which it has reached its destination.

The terms which he introduced, endometrioma and endometriomyoma, would tell a great deal were they always correct. For instance, it is probable from recent studies of Sampson that some of these growths do not arise from endometrium but from endosalpinx. Also, is it certain that one is dealing with a true tumor?

In an article on adenomyoma of the rectovaginal space and its association with ovarian tumors containing tarry material, Archibald Donald stated that the blood in the cysts closely resembles retained menstrual blood, such as is seen in hematocolpos or hematometra. He regarded their power of burrowing as evidence that they originated near the hilum of the ovary. Shaw and Addis recorded similar observations and tentatively agreed with Sampson concerning the etiologic significance of the ovarian cyst.

Lochrane, in reporting a case of decidual reaction in adenomyoma of the rectovaginal septum, said that it is probable that adenomyomas owe their inception to an antecedent inflammation in the tissues of origin. In the following year (1923), however, in a communication on decidual reaction in diffuse endometriomyoma of the pregnant uterus, he was of the opinion that it is possible for small cell fragments to be carried from the uterine to the peritoneal cavity by ascending currents which have been shown by Bond to be in action continually in the female genital tract. He considered the decidual reaction in the ectopic foci as one of the strongest arguments in favor of their being müllerian tissue.

Bailey (1924) was in agreement with Sampson's idea that endometrial tissue or tubal epithelium can be carried along the lumen of the tube during menstruation into the abdominal cavity in which it can be implanted on peritoneum. He suggests the term müllerianoma for the condition which develops. He does not believe that perforation of a menstruating cyst of the ovary ever takes place, but that the affected ovary becomes adherent to adjacent structures at a stage when slight hemorrhagic erosion or excavation has occurred on its surface, sufficient to form adhesions. The cyst, he believes, is formed by "excavation" and not by dilatation secondary to retention of secretion and blood.

The publication of Sampson's papers led to a more intensive study by American gynecologists of all forms of chronic adhesive pelvic disease. The thorough studies of Cullen on the diffuse adenomyoma of the uterus has given that lesion its correct interpretation as being derived directly from an invasion of the myometrium by endometrium. Cullen's views on adenomyomas in general have been accepted by most gynecologists for many years, his book on the subject being illustrative of many types of this kind of growth. The announcement of the implantation theory by Sampson was followed by a period of relative silence on the subject on the part of American gynecologists, since it had certain features which at first were reconciled with difficulty with the existing state of knowledge of pelvic disease in the female. It implied a frequent passage of menstrual blood through the tubes into the abdominal cavity, something which had been rarely if ever seen. It assumed that epithelium cast off at the menses is not all dead and that some live cells become implanted on pelvic peritoneum and grow, much like malignant epithelial cells disseminated from a malignant ovarian cyst. The views of Cullen were eagerly awaited.

At the fiftieth annual meeting of the American Gynecological Society in Washington, D. C., 1925, a symposium was held on misplaced endometrial tissue. At this meeting Keene reported two cases of invasion of the wall of the bladder by menstruating endometrial tissue in patients who also had perforating ovarian (Sampson's) cysts. Cystoscopic

examination revealed an area of intensely red mucosa in which several vesicles with blue discoloration were found. In one case superficial ulcers were present over the vesicles, which proved on histologic examination to be typical menstruating endometrium-like tissue.

Heaney reported two cases of "adenoma of endometrial origin in the laparotomy scars following incision of the pregnant uterus (cesarean section)." The menstruating tissue in the scars was regarded as brought to the operative wound by the operator, where it became engrafted. These growths in laparotomy scars gave clinical evidence of their presence in from a few weeks to several years. Usually they became enlarged and tender during each menstrual flow. Heaney found reports of seven similar cases in the literature.

Danforth reported one case of "adenoma of the abdominal wall." He mentioned various ways in which the tissue could be transplanted to the abdominal wound, such as by dragging the membranes over the wound in delivering the placenta. Laparotomy pads could also serve as the vehicle to convey the loose epithelial cells.

Sampson summed up his knowledge of ectopic endometriosis, and emphasized particularly the likeness in distribution of endometrial implants to carcinoma implants, that endometrium can invade blood and lymph channels, and that it can lodge in the same loci as carcinoma cells which gain entrance to the peritoneal cavity.

Graves reported four cases of ectopic adenomyomas in which the patients were treated by oophorectomy which resulted in retrogression of the ectopic foci. He urged the logic of ovarian extirpation in the treatment of the patient, indicating too that it is a sort of therapeutic test of the endometrial character of these growths. He mentioned Sitzenfrey's experience in which complete hysterectomy caused disappearance of an infiltrating adenomyoma. Graves at that time was inclined to agree with Sampson that the great majority of these growths result from endometrial implants, although he considered that the adult peritoneum could give rise to umbilical adenomyomas. He stated that the postoperative adenomyomas could have arisen only from implants.

In the discussion of the several papers, Dr. James Ewing drew attention to the fact that the pelvic tissues constitute a potpourri of tissue abnormalities of various types, including metaplasias of peritoneal cells, and about the uterus and tubes are tissue rests difficult to classify. He felt that Sampson's theory would not account for all the aberrant structures, particularly the appendiceal fragments which he thought were buried too deeply to have arisen by implantation. He stated:

> I would be willing to accept as endometrial transplants those cases in which the structure is typical, in some instances even perhaps without endometrial stroma, and where the clinical history indicates that some violence has been done to the endometrium or tubal mucosa which can reasonably account for a transplant or

misplacement of endometrial mucosa. . . The fact that endometrial tissue can be transplanted by mechanical insults is certainly a warning to the gynecologist in handling these organs. . . The evidence that a peculiar group of tumors arise from these transplants seems to be satisfactory and clears up the nature of a puzzling series of neoplastic lesions in the pelvis.

The views of Cullen are available only in his discussion of the foregoing papers, and are as follows:

The glands of adenomyomata of the uterus usually develop from the uterine mucosa. Adenomyomata of the round ligament appear to be due to embryonic inclusions. Adenomyomata of the umbilicus are evidently due to embryonic inclusions. Adenomyomata in abdominal scars are due to transplants. Adenomyomata developing on peritoneal surfaces in or near the pelvis are still in "No man's Land" with much evidence that they may owe their origin to transplants.

ECTOPIC DECIDUA

The reaction of the endometrial stroma to pregnancy—the transformation of the small spindle cells into decidual cells—is characteristic of endometrium; hence it should be expected that ectopic endometrium, whatever its location, could show a similar stromal change. And such is the case. In 1905, Amos reported decidua formation in the mucous membrane of a uterine adenomyoma associated with a similar change in a connective tissue tumor of the abdominal wall. Cullen, in 1920. reported decidua of pregnancy in an endometrial growth in the rectovaginal septum. Sampson, in 1922, and Lochrane, in 1923, made similar observations. In 1924, Frederica Winestine reported decidua in the wall of an endometrial ovarian cyst (adenoma endometrioides ovarii). In 1926, Schiller and de Jong carefully studied ectopic decidua in the light of the recent work on endometriosis. Williams, in his textbook of obstetrics, discusses ectopic decidua, small foci of which without accompanying epithelial structures have been found in the pouch of Douglas, omentum, the appendix serosa, the perisinous tissue of the pelvic lymph nodes, diaphragmatic peritoneum and in adhesions about the uterus, tubes and ovaries. White has reported an example of decidual reaction in an adenomyoma of the rectovaginal septum.

Wilfred Shaw stated that the factor which controls the formation of decidua is produced by the corpus luteum. He found decidual cells in the ovaries in eight of thirty-three cases in the twentieth to twenty-eighth day of the menstrual cycle. He concluded: 1. Ectopic decidual cells are widely distributed in normal uterine pregnancy. 2. Decidual cells are also found independently of pregnancy in the premenstrual phase of the menstrual cycle, in the endometrium and in the ovary. 3. The property of decidual reaction is inherent in certain cells which are derived from the subcelomic mesoblast.

Nevertheless, it cannot be accepted as proved that decidua can be formed in any condition other than pregnancy. In the premenstrual

phase and in certain low grade chronic inflammatory conditions of the endometrium, a swelling of the stromal cells occurs which might be called deciduoid, but I believe that a typical decidual cell is seen only in pregnancy.

Suffice it to say that the essential endometrial character of the growths under discussion has been further demonstrated by the decidual reaction in their stroma. It is usually impossible to be certain of the origin of glandlike spaces and small cysts in pelvic tissues unless they are accompanied by typical endometrial stroma. Another problem needs solution, however, and that is the question concerning the origin of microscopic foci of decidual cells just beneath the peritoneum, which have apparently never been accompanied by glands. There are three main possibilities: 1. They represent congenital rests of deciduopotential cells. 2. They result from the implantation of stromal cells cast loose in much the same manner as the uterine epithelial cells during menstruation. 3. They are caused by some cells of fibroblast type in the subserosa being acted on by an ovarian hormone which is circulating in the peritoneal lymph or is brought by the blood vessels. Not enough data are available to permit a definite answer at this time concerning the genesis of these deposits.

POSTOPERATIVE ENDOMETRIOSIS

Postoperative invasions of the abdominal wall by endometrial tissue have been noted in increasing numbers since the question of endometrial implantation was raised. The operation most likely to be followed by this complication is cesarean section, but there are instances of simple suspension of the uterus, and even operations not involving the uterus at all in which infection of the tissue of the abdominal wound occurred.

Lemon and Mahle (1925) reported nine cases of postoperative invasion of the abdominal surgical wound. The operations were ventral suspension of the uterus, internal Alexander operation, shortening of the uterine ligaments, hysterectomy and oophorectomy (in the last operation one ovary was left). The gross characteristics of the abdominal adenomyoma were said to be as clearcut as those of the wall of the uterus. The largest was 6 by 4 by 4 cm., extremely firm and with the consistence of a myoma. The skin and previous operative scar may be dimpled from the invasion of the tumor lying beneath the surface of the skin. In the substance of the tumor were cystlike spaces which were filled with dark chocolate-brown fluid. Histologically, the gland spaces were typically uterine, usually with characteristic uterine stroma. Bands of smooth muscle were present in the stroma and degenerative changes in the skeletal muscle. Old and recent menstrual blood was seen in the stroma and lumen of the glands and cysts. In one case tuberculosis was also present. In none of their cases did

adenomyoma exist in the uterine wall, nor was it possible by serial sections to trace adenomyoma from the uterine mucosa out into the growth in the abdominal wall. The authors concluded from a study of their material that the accepted hypotheses with regard to the production of adenomyomas in the uterus and tubes would not explain adenomyoma of the abdominal wall. They regarded as logical a suggestion of Judd's, that in the various operations on the uterus the needle and suture had transplanted endometrial cells from the uterus to the abdominal wall.

Heaney, Schwartz and Danforth also reported endometriosis in the laparotomy scars following cesarean section. Danforth regards the possibility of transfer of endometrium by suture in ventral suspension as somewhat fanciful. Nicholson also thinks that that method is unlikely. Schwartz said that he believes in implantation by the operative procedure.

Sampson referred to a case of adenomyoma seen by Dr. F. B. Mallory which developed in an abdominal scar several years after cesarean section.

Dietrich described a case of adenoma formation in the abdominal scar following ventral fixation of the uterus. He referred to six previously reported instances as being the only others in the literature: those of Meyer, von Franque, Klages, Fraas, Lauche and Bergmann. He agreed with Meyer that the gland structures originate from peritoneum, and he showed photomicrographs which he regarded as illustrative of this mode of development of endometrial tissue.

Nicholson, writing on endometrial tumors of laparotomy scars, stated that they are restricted to the lower half of the abdominal wall, the highest point being the umbilicus. He calls them "acquired accessory uteri." He regards the peritoneal metaplasia theory as the most generally applicable, its acceptance offering the fewest difficulties; also that it is contrary to experience to assume that the tumors have a congenital origin, or are from congenitally predisposed cells. He said: "There is no reason why every differentiation undergone in development of tissues of the embryo should not be repeated during the whole life of the individual in pathologic states." The celomic epithelium gives rise to endometrium in utero; hence it can do so in the adult if the right stimulus is present, namely, the ovarian influence.

Shaw reported a case of adenomyoma of the round ligament; the patient menstruated through the abdominal incision, and burrowing hemorrhages in the abdominal wall in the inguinal region resulted.

UMBILICAL ENDOMETRIOSIS

Another interesting type of endometriosis is sometimes observed in the umbilical region without a previous laparotomy incision. Mintz,

in 1899, described an "adenom des Nabels," and in the same year Green reported a similar case. In a series of articles on umbilical tumors containing uterine mucosa or "remnants of Müller's ducts," Cullen described these growths and summarized the knowledge of them up to the year 1922. Edwards and Spencer described the tumor thus:

> The adenomyoma of the umbilicus occurs in the umbilical cicatrix of women between the ages of 35 and 45, reaching its full development within a few months after its appearance and characterized clinically by redness, swelling, pain, and in some instances, by bleeding from the tumor at the menstrual period.

The tumors vary in diameter from 0.5 to 3 cm., projecting from the umbilical depression, at times completely filling the cavity. They are covered by normal or slightly thickened, sometimes atrophic, epidermis which is often pigmented. Small cysts filled with dark brown fluid are visible occasionally through the skin as bluish areas. On section, much dense connective tissue separates the small cysts with their pigmented contents. Histologically, the cysts and smaller glands are like those of the endometrium with typical menstrual hemorrhage into the stroma.

Köhler recently described a typical case which he said is the thirty-second in the literature. There were brownish discharge from the navel and increase in size and hardness of the tumor in the premenstrual period, with severe pain. Not so much as a thin strand connected the tumor with the peritoneum. Köhler was inclined to accept the theory that these tumors originate in true uterine gland tissue transported by the lymph stream.

At the meeting of the American Association of Pathologists in 1927, Weller reported two cases of menstruating umbilical tumors. In his abstract, he stated:

> These tumors showed the characteristic endometrial structure in respect to both glandular elements and surrounding cellular stroma but no smooth muscle belonging to the tumor was found in either instance. The absence of such muscle has been mentioned in other reported cases and the term "adenomyoma" is, therefore, a misnomer. Greater importance is attached to these tumors from the standpoint of the evidence which they afford as to the histogenesis of this group than to their clinical aspects. Of the latter, the most important is recognition of the fact that they are neither primary melanoblastomas nor metastases of malignant intra-abdominal neoplasms, conditions with which they are usually confused clinically. As to histogenesis, the occurrence of this tumor at the umbilicus cannot be satisfactorily explained as being due to endometrial implantation or to lymphogenous or hematogenous metastasis from proliferating endometrial growths in the pelvis. It throws doubt upon the theories of Sampson in regard to the origin of this entire group and seems to find its best explanation in a theory based upon a serosal origin.

Whenever a pathologic distribution of a tissue or a widespread infection of the body occurs, the logical procedure is to try to find

one explanation for the many similar lesions. When this cannot be done, it is just as logical to invoke other causative factors. Implantation of endometrial fragments on peritoneal surfaces will explain a large majority of ectopic endometrial growths. Subperitoneal endometriosis in the broad ligament and possibly in the groin and some cases of subserous endometriosis of the uterus itself may be due to metastasis by way of the veins or lymphatics. I have seen one undoubted instance of implantation of endometrium in an umbilical hernial sac. Possibly inguinal endometriosis represents endometrial implantation in an inguinal hernial sac. A hernial sac, if small enough, can be obliterated by a pathologic (inflammatory) process within it; hence the absence of a sac in umbilical or inguinal endometriosis does not necessarily rule out its one time presence. Umbilical hernia is much more common than umbilical endometriosis. The fact, however, that ectopic but otherwise normal tissue is frequently found in the midline of the body may offer a suggestion concerning another possible explanation of endometrial tissue in the umbilicus; it may be congenitally misplaced, as Cullen believes.

COMMENT

Endometrial heterotopia per se is not of the nature of a true neoplasm, although the fact that endometrial glands and stroma can invade a tissue has been used by some as sufficient ground for so regarding it; hence the terms endometrioma and müllerianoma. A more important question arises, however. It is not an uncommon experience in pathologic sections for one to encounter a cancerous change in a focus of misplaced tissue, for instance, epidermoid carcinoma in a wen, or in an ovarian dermoid, and sarcomatous reactions in mixed tumors. According to Cohnheim's hypothesis, a cancer is prone to develop in congenitally misplaced cells, and in the sense of Ribbert, postnatal displacements would be likely foci for the birth of a tumor.

Whether or not Sampson is right in his explanation of the route by which endometrium reaches extra-uterine situations, a considerable field for study is opened up by his studies; in particular, the origin of the epithelial tumors of the ovary that do not arise in follicular or luteal epithelium. The pseudomucinous cystadenoma, the papillary cystadenoma and carcinoma and even the solid carcinomas of the ovary need more thorough study. The average ovarian tumor which reaches the surgeon usually is fairly large, and in the average busy pathologic laboratory only a few sections are made for histologic examination. It is reasonable to expect that only a minimum of information can be elicited by this manner of laboratory routine.

Sampson has studied sixteen cases of ovarian carcinoma, examining many sections from various parts of the tumors. In seven specimens,

he found endometrium-like tissue in the ovary "bearing the same histological relation to the malignant growth that the benign uterine mucosa bears to the adenocarcinoma arising in the body of the uterus. . . . . In all seven instances the histologic structure of the carcinoma was similar to that found in some cancers of the body of the uterus."

It is well recognized that many papillary carcinomas of the ovary look like the papillary adenocarcinoma of the fundus uteri. A cancerous change in endometrial implants, particularly in the ovary, which is unusually good soil for such tissue, would seem a reasonable possibility. Sampson has demonstrated the neoplastic transformation of ectopic endometrium in the ovary. He has also made another observation. In cases of adenocarcinoma of the fundus uteri, fragments of the tumor were found in the tube following curettage. These fragments were histologically alive. He argues that if implantations of tumor can occur following rupture of a malignant ovarian cyst, why should it not be possible for tumor cells to be implanted following tubal transportation from a uterine carcinoma, subsequently with the development of an ovarian carcinoma? He draws attention to the danger of curettage in carcinoma of the body of the uterus as a means of disseminating tumor cells through patent tubes.

Sampson naturally asks, too, if cancer particles can be transported in the tubes why cannot pieces of normal menstruating endometrium? Van Oettingen and Linden insist that the implantation hypothesis is based on an impossibility, that the tube lumen is not wide enough to allow fragments of tissue to pass through it. Schiller and von Franque have both recorded observations of finding free cancer particles in the tube of a specimen of carcinoma of the body of the uterus, and if the tube is wide enough for malignant cells it certainly is for normal or any other kind of cells.

A recent study of Sampson's on metastatic or embolic endometriosis deals with the menstrual dissemination of endometrial tissue into the venous circulation. This work was based on a previous investigation made in 1918, when he demonstrated by injections of bismuth the existence of "receiving sinuses" radiating from the base of the endometrium into the myometrium. He showed that if these sinuses were exposed, as by curettage, and the uterus relaxed, fluid and small particles of solid material could easily escape from the uterine cavity into them when the pressure in the uterus was greater than that in the sinuses, thus explaining one way by which puerperal infection may result or placental cells gain access to the extra-uterine veins.

Sampson applied the methods used in the foregoing study, to the menstruating uterus. In a well illustrated article, he showed clearly that (1) fragments of endometrial tissue, at times, are disseminated

into the venous circulation during menstruation, from the mucosa lining the uterine cavity and also from the ectopic endometrial foci; (2) metastatic or embolic endometriosis arises from the implantation of these emboli in nearby veins; (3) endometrial tissue set free by menstruation, therefore, sometimes not only is alive but may actually continue to grow if transferred to situations favorable to its existence.

The import of his observations is obvious. He showed conclusively that endometrial tissue set free at menstruation is not all dead, some is alive and capable of further growth under favorable conditions. He also indicated another route—the intravascular, more specifically the intravenous—for the dissemination of endometrial emboli. So far this pathway can be invoked most advantageously in cases of intraligamentary and inguinal endometriosis. That many emboli reach the lung must be assumed, although no growth of endometrial type has ever been found in the lung. I have injected a fine suspension of endometrium from rabbits in heat into the vein of the ear of the same rabbits, but after from twenty-four to forty-eight hours the cells while held up in the capillaries of the lung were degenerated or entirely necrotic and enmeshed in fibrin.

Much of the discussion of the various phases of endometriosis has centered about the point of whether or not any of the tissue cast loose in the uterus at menstruation is alive. The plausibility of Sampson's theory is greatly affected by the answer to this question. Novak of Cullen's clinic stated categorically that the cells cast loose during menstruation are all dead and hence could not be implanted on anything. Later he tempered this statement by saying that if they are not dead, they are at least very "sick" and hence could not be expected to grow again. Of course, if the epithelium is dead or nearly so, it could not produce new endometrium, on either peritoneal surfaces or wherever it might be transported by the lymph or blood streams.

At present there are two methods available for determining whether or not cells are alive. The first consists in fixing the nucleus and cytoplasm by appropriate agents, then staining with certain dyes and examining under the microscope. The other procedure is an attempt to grow the cells in vitro or to observe their movements or ciliar action in proper mediums on a glass slide.

Using aseptic precautions Cron and Gey removed the bloody fluid from a menstruating uterus. In vitro cultures gave what these observers regarded as definite evidence that some of the epithelial cells from the endometrium are viable when thrown off by menstruation, and capable of proliferation in the test tube. This is a crucial experiment and, together with Sampson's histologic studies of intravascular invasion of endometrium, furnishes the last link in the chain of evidence that among the cells cast loose during menstruation are many living

epithelial cells. With that fact established, it is not difficult to believe that when transported to favorable soil these cells can develop into functioning tissue of endometrial type.

BIBLIOGRAPHY

Amos, J.: Ztschr. f. Geburtsch. u. Gynäk. **54**:171, 1905.

Bailey, K. V.: J. Obst. & Gynec. Brit. Emp. **31**:539, 1924.

Barker, A. E.: Lancet. **2**:128, 1913.

Bell, W. B.: J. Obst. & Gynec. Brit. Emp. **29**:443, 1922; Personal communication (on experimental endometriosis).

Casler, D.: Tr. Am. Gynec. Soc. **44**:69, 1919.

Cron, R. S., and Gey, G.: Am. J. Obst. & Gynec. **13**:645, 1927.

Cullen, T.: Johns Hopkins Hospital Reports, 1896, vol. 6; Adenomyoma of the Uterus, Philadelphia, W. B. Saunders Company, 1908; Distribution of Adenomyomas Containing Uterine Mucosa, Arch. Surg. **1**:215 (Sept.) 1920; Diseases of Umbilicus, Philadelphia, W. B. Saunders Company, 1916; Surg. Gynec. Obst. **35**:257, 1922; Am. J. Obst. & Gynec. **10**:732, 1925.

Danforth, W. C.: Am. J. Obst. & Gynec. **10**:630, 1925.

Dietrich, A.: Arch. f. Gynäk. **120**:306, 1923.

Donald, A.: J. Obst. & Gynec. Brit. Emp. **32**:529, 1925.

Dossena, P.: Tumori. **12**:291, 1926.

Edwards, C. R., and Spencer, H. R.: Adenomyoma of Umbilicus, Arch. Surg. **11**:684 (Nov.) 1925.

Ewing, J.: Am. J. Obst. & Gynec. **10**:730, 1925.

Goddard, S. W.: Surg. Gynec. Obst. **249**:9, 1909.

Graves, W. P.: Am. J. Obst. & Gynec. **10**:665, 1925.

Green, C. D. vide Cullen, Diseases of Umbilicus, 1916.

Halban, J.: Wien. klin. Wchnschr. **37**:1205, 1924.

Heaney, N. S.: Am. J. Obst. & Gynec. **10**:625, 1925.

Hedley, J. P.: J. Obst. & Gynec. Brit. Emp. **18**:293, 1910.

Herly, L.: Surg. Gynec. Obst. **626**:39, 1924.

Hesselberg, C.; Kerwin, W., and Loeb, L.: J. M. Research. **38**:11, 1918.

Iwanoff, N. S.: Monatschr. f. Geburtsh. u. Gynäk. **7**:295, 1898.

Jacobsen, V. C.: Arch. Surg. **5**:281, 1922; Am. J. Obst. & Gynec. **6**:257, 1923; Arch. Path. **1**:169, 1926.

Janney, J. C.: Am. J. Obst. & Gynec. **10**:630, 1925.

de Jong, J.: Virchows Arch. f. path. Anat. **262**:735, 1926.

Katz, H., and Szenes, A.: Zentralbl. f. Gynäk. **44**:2400, 1924.

Keene, F.: Am. J. Obst. & Gynec. **10**:625, 1925.

Kitai, I.: Arch. f. Gynäk. **124**:178, 1925.

Kohler, R.: Zentralbl. f. Gynec. **51**:2201, 1927.

Lahm, W.: Ztschr. f. Geburtsh. u. Gynäk. **85**:85, 1922.

Lauche, A.: Virchows. Arch. f. path. Anat. **243**:298, 1923; Deutsche med. Wchnschr. **19**:595, 1924.

Lochrane, C. D.: J. Obst. & Gynec. Brit. Emp. **3**:443, 1923.

Lockyer, E. C.: Fibroids and Allied Tumours, New York, The Macmillan Company, 1918 (this contains most of the references to the early literature of adenomyoma).

Lemon, W. S., and Mahle, A. E.: Ectopic Adenomyoma, Arch. Surg. **10**:150 (Jan.) 1925.

Mintz, W.: Deutsche Ztschr. f. Chir. **1**:545, 1899.

Mahle, A. E.: Surg. Gynec. Obst. **33**:57, 1921.

Meyer, R.: Ztschr. f. Geburtsh. u. Gynäk. **49**:404, 1903; Virchows Arch. f. path. Anat. **144**:487, 1909; Zentralbl. f. Gynäk. **51**:1482, 1927; Virchows Arch. f. path. Anat. **250**:595, 1924.

Michon, L.: Lyon chir. **24**:313, 1927.

Nicholson, G. W.: J. Obst. & Gynec. Brit. Emp. **33**:620, 1926.

Norris, C. C.: Am. J. Obst. & Gynec. **1**:831, 1921.

Novak, E.: Am. J. Obst. & Gynec. **10**:734, 1925.

Novak, E., and Darner, M. D.: Am. J. Obst. & Gynec. **9**:295, 1925.

O'Keefe, C. D., and Crossen, R.: Missouri State M. J. **13**:330, 1927.

Pick, L.: Arch. f. Gynäk. **76**:2, 1905.

Ries, E.: Ztschr. f. Geburtsh. u. Gynäk. **37**:518, 1897.

Runge, E.: Arch. f. Gynäk. **69**:190, 1903.

Russell, W. W.: Bull. Johns Hopkins Hosp. **10**:8, 1899.

Sampson, J. A.: Am. J. Obst. & Gynec. **78**:2, 1918; ibid. **4**:5, 1922; Boston M. & S. J. **186**:445, 1922; Arch. Surg. **5**:217 (Sept.) 1922; Surg. Gynec. Obst. **38**:287, 1924; Arch. Surg. **10**:1 (Jan.) 1925; Am. J. Path. **3**:93, 1927.

Semb, C.: Acta Obstet. et Gynec. Scandinav. **5**:200, 1926.

Shaw, W., and Addis, W. R.: J. Obst. & Gynec. Brit. Emp. **32**:344, 1925.

Schiller, W.: Arch. f. Gynäk. **129**:425, 1926.

Schwartz, O. H.: Am. J. Obst. & Gynec. **13**:330, 1927.

Semmelink, R., and de Jong, J.: Monatschr. f. Geburtsh. u. Gynäk. **22**:234, 1905.

Smith, R.: Am. J. Obst. & Gynec. **1**:240, 1920.

Spirito, F.: Arch. di ostet. e ginec. **14**:1, 1927.

Stilling, H.: Beitr. z. path. Anat. u. z. allg. Pathol. **47**:499, 1910.

Stubler, E.: Deutsche. med. Wchnschr. **50**:908, 1924.

Van Oettingen, K., and Linden, H.: Arch. f. Gynäk. **122**:718, 1924.

Vogt, E.: Med. Klin. **20**:884, 1924.

White, R. J.: Am. J. Obst. & Gynec. **10**:112, 1926.

Williams, J. W.: Textbook of Obstetrics, New York, D. Appleton & Company, 1917.

Winestine, F.: Arch. Surg. **8**:772, 1924.

Wolf, E. H.: Arch. f. Gynäk. **84**:211, 1908.

Wulfing, H.: Ztschr. f. Geburtsh. u. Gynäk. **44**:1, 1901.

Notes and News

Necropsies at the University of Minnesota.—E. T. Bell reports (*J. A. M. A.* **90**:896, 1928) that 1,353 necropsies were performed by the department of pathology of the University of Minnesota in 1927. Of the bodies on which necropsy was performed, 1,023 came from Minneapolis and represented 19 per cent of those who died in that city in 1927, excluding the stillbirths. Similar statistics from other sources would throw interesting light on the relative frequency of necropsies and on the conditions that influence the obtaining of necropsies.

Death of Lydia M. De Witt.—Lydia M. De Witt, associate professor emeritus of pathology in the University of Chicago and a member of the Otho S. A. Sprague Memorial Institute until her retirement three years ago, died on March 10, 1928. While connected with the department of anatomy of the University of Michigan she made important studies of the pancreas and of the sinoventricular connecting system of the heart. At the Sprague Institute she worked on the chemistry and chemotherapy of tuberculosis. Her work was careful and well substantiated, as shown particularly in her conclusions about the treatment of tuberculosis with copper and gold.

Violation of So-Called Professional Secrecy by Pathologist.—From Berlin comes the report that in a lecture to medical students a professor of pathologic anatomy mentioned the name of the person whose organs were demonstrated. The person in question had figured frequently in the newspapers as a criminal. The newspapers brought the circumstance to the attention of the minister of public instruction, who announced that to mention the name of the deceased in demonstrating his organs is a violation of the obligation of professional secrecy and shows lack of sound judgment.

Death of J. Danysz.—J. Danysz of the Pasteur Institute in Paris died recently. His name is associated with a paratyphoid organism used for killing rats (Danysz virus, *Bacterium danysz*) and with the decrease of the neutralizing power of antitoxin when toxin is added to it in divided portions instead of all at once (Danysz phenomenon).

Archives roumaines de pathologie expérimentale et de microbiologie.—This new journal is edited by Professor Cantacuzène in Bucharest. It is published by Masson and Cie, in Paris, as a quarterly. The first number has just made its appearance.

Another Death Among Workers on Rocky Mountain Spotted Fever.—During the course of the investigations on Rocky Mountain spotted fever by the Public Health Service, four workers have lost their lives from the disease, contracted in connection with their official duties. A. Leroy Kerlee was the most recent worker to lose his life in this way. He was employed as a bacteriologist in the Public Health Service Laboratory at Hamilton, Mont. He was a recent graduate of the Montana State College, and had been in the service since September, 1927. Those who had previously lost their lives in this work were T. B. McClintic, who died in 1921; W. E. Gettinger, a laboratory assistant, who died in 1922, and G. H. Cowan, a field assistant, who died in 1924.

HIDEYO NOGUCHI, M.D.
1876-1928

Obituary

HIDEYO NOGUCHI, M.D.

1876-1928

Dr. Hideyo Noguchi, of the Rockefeller Institute for Medical Research, died at Accra, West Africa, Monday, May 21, 1928. He gave his life for humanity in a scientific endeavor to discover the relation between South American and African yellow fever. The results of the bacteriologic studies made by him in South America proved inapplicable to yellow fever as it exists in West Africa. Although not himself in the best of health, and at an advanced age, he insisted, against the advice of many friends, in undertaking the arduous expedition. His work in Africa was completed, and he planned to sail for New York on May 19, when, a few days before, he was stricken with yellow fever. He had weighed well the dangers of the undertaking and went, on what unhappily proved the last of an extraordinary number of successful scientific expeditions, prepared to make the extreme sacrifice. Fortunately, the results of his studies will not be lost. Others will take them up where he was compelled to leave them, although it is too much to expect that any one can carry them to final completion and publication as brilliantly as he would have done, had he been spared.

Dr. Noguchi was born on Nov. 24, 1876, at Inawashiro, Yama County, Fukushima, Japan. He studied medicine at the Tokio Medical College from 1893 to 1897 and received the license to practice medicine from the Japanese Government in 1897. From 1898 to 1900, he was assistant in the Government Institute for Infectious Diseases, Tokio, and during this period he held a lectureship in bacteriology at the Tokio Dental College.

Dr. Noguchi came to the United States in 1900 and joined the pathologic staff of the University of Pennsylvania, under Dr. Simon Flexner. He remained at the University of Pennsylvania until 1903, having been appointed research assistant of the Carnegie Institution of Washington, and then continued his studies at the Statens Serum Institute in Copenhagen, under Dr. T. Madsen. In 1904, at the founding of the laboratories of the Rockefeller Institute in New York, he joined the original staff of that institution and became one of its original members. In 1911 he married Mary Dardis, who survives him.

Dr. Noguchi was awarded a titular professorship by the department of education of the Imperial Japanese Government in 1911. He was the recipient of many honorary degrees, including the Ph.D. degree of the Imperial University of Tokio in 1914. In 1923, he was elected to

membership in the Imperial Academy of Japan, and in 1924, he was awarded the medal of the Society of Japanese as one of the ten greatest Japanese. Among the institutions conferring honors on him are Yale and Brown Universities in the United States and the Sorbonne in Paris. Numerous honors were conferred on him by various South American countries where he carried on his researches on yellow fever. In 1921, he received the John Scott Medal from the City of Philadelphia. He was also a chevalier of the Legion of Honor, a Knight of the Royal Order of Isabella of Spain, of the Royal Order of Dannebrog (Denmark) and of the North Star (Sweden). In 1915, he received the Emperor's Medal and Premium from the Imperial Academy of Japan, and the Order of the Rising Sun was conferred on him. He was a member of many scientific societies in the United States and in foreign countries.

Dr. Noguchi was a great bacteriologist and ranks among the most eminent of all time in that field. His earlier scientific work was on the biology of the venoms and antivenenes, the Carnegie Institute of Washington publishing his monograph on "Snake Venoms" in 1909. Later, he studied with extraordinary success the bacteriology of the spirochetes, a number of which he cultivated artificially for the first time. He was the first to demonstrate *Spirochaeta pallida* in the brain of paralytic persons and to transmit syphilitic infection to rabbits by means of brain tissue from persons succumbing to general paralysis. In 1915, he first cultivated a bacteria-free vaccine virus in the tissues of rabbits, an accomplishment of great practical value in providing a pure virus for purposes of vaccination. In 1918, he served on the Yellow Fever Commission sent by the International Health Board of the Rockefeller Foundation to Guayaquil, Ecuador, and it is noteworthy that he lost his life while investigating yellow fever in West Africa for the Rockefeller Foundation, to which he was loaned by the Rockefeller Institute.

In recent years Dr. Noguchi isolated a micro-organism *(Bartonella bacilliformis)* from the blood of persons who died from Carrion's disease (Oroya fever) and the associated skin nodules, verruga peruana, of Peru. He was able to reproduce the human disease in monkeys by means of the cultures obtained. This achievement settled the long disputed problem of the relation of Oroya fever to verruga.

During 1926, Dr. Noguchi cultivated from the eyes of American Indians suffering from trachoma a bacillus which reproduces trachoma in rhesus monkeys and in chimpanzees.

In the death of Dr. Noguchi, bacteriologic science has lost one of its most brilliant and original investigators.

Abstracts from Current Literature

Pathologic Physiology

THE EFFECT OF THYROID THERAPY ON CHILDREN. ANNE LAFFER and PHILIP COHEN, Am. J. Dis. Child. **35**:205, 1928.

In normal children thyroid therapy did not influence the basal metabolic rate, but seemed to stimulate growth processes. In children with hypothyroidism, the response was similar to that in adults with that condition. The theory offered to explain the difference in response between normal children and normal adults is that thyroid, being a metabolic catalyst, increases the phase of metabolism which is dominant in the individual, anabolic or growth processes in the child and catabolic or oxidative processes in the adult. The basal metabolic rate in children is considered an unreliable criterion of the presence of thyroid disease and of the effect of thyroid therapy.

PEARL M. ZEEK.

THE EFFECT OF PARATHYROID EXTRACT ON MINERAL METABOLISM IN INFANTILE TETANY. ALFRED T. SHOHL, A. M. WAKEMAN and E. Y. SHORR, Am. J. Dis. Child. **35**:392, 1928.

The authors' conclusions are as follows: Small amounts of parathyroid extract were administered in two cases of infantile tetany. The drug had little effect on one infant. The second infant showed a control of the symptoms and an improvement as measured by clinical and chemical results. This improvement is transitory and disappears when treatment is stopped. The alteration is brought about without gross changes in the calcium and phosphorus metabolism. During the period of administration of parathyroid extract with relief of symptoms, there was a normal excretion of sodium and potassium. During the relapse following withdrawal of parathyroid extract, the excretion of sodium increased and potassium was retained.

PEARL M. ZEEK.

THE RELATIONSHIP OF GLYCOGEN FORMATION IN THE MUSCLES TO THE PANCREAS AND TO EPINEPHRINE. YOUNG O. CHOI, Am. J. Physiol. **83**:406, 1928.

The intravenous injection of dextrose into eviscerated spinal cats did not affect the glycogen content of the muscles of the legs over a period of two or three hours. If the injection was accompanied by that of insulin, the muscular glycogen was increased. In noneviscerated animals, the injection of dextrose alone brought about this increase. Since the effects of pancreatectomy were similar to those of general visceral removal, the writer concludes that the responsible organ is the pancreas. Epinephrine was found not to stimulate the breakdown of muscular glycogen, nor did it cause hyperglycemia in eviscerated animals.

H. E. EGGERS.

THE EFFECT OF ELIMINATING THE SPHINCTER OF THE COMMON BILE DUCT UPON EMPTYING OF THE GALL-BLADDER. W. C. EMERSON and L. R. WHITAKER, Am. J. Physiol. **83**:484, 1928.

In dogs and cats, the possible sphincteric action of the intestinal musculature at the point of discharge of the common bile duct was eliminated by the insertion of a cannula, and after the peritoneal cavity was closed, the conduct of the gallbladder was observed by the roentgen ray. It was found that in spite of this procedure, the gallbladder retained its contents for hours, or until the animal was

fed, when normal discharge took place. So that the emptying of the gallbladder is apparently not the result of its elasticity taking effect after sphincteric relaxation, but involves some other factor, presumably muscular contraction.

H. E. Eggers.

Micro-Injection Studies of Capillary Permeability. E. M. Landis, Am. J. Physiol. **83**:528, 1928.

The effects of lack of oxygen of high carbon dioxide tension and of increased hydrogen ion concentration on capillary permeability were studied in single capillaries of the frog's mesentery, by direct measurement of fluid movement in cubic microns per square micron of capillary wall per second, with measurement of capillary pressure. Immediately after a three minute period of oxygen deprivation, the rate of filtration through the capillary wall was approximately quadrupled. Along with this there was increased escape of protein, to the extent of reducing the effective osmotic pressure of the plasma proteins by about one half. The movement of fluid through the asphyxiated wall was directly proportional to the difference between capillary pressure and the effective osmotic pressure of the plasma proteins, so that apparently the vessel wall acted merely as a passive filter. With return of circulation, there was a rapid recovery of relative impermeability. Half saturation with carbon dioxide of the Ringer's solution in which the mesentery was bathed did not effect the movement of the fluid; complete saturation increased the rate of movement slightly, but was without effect on permeability to protein. Increase of hydrogen ion concentration was without appreciable effect until physiologic bounds were passed.

H. E. Eggers.

The Bile-Expelling Mechanism of the Guinea-Pig. C. E. Burget and R. J. Brocklehurst, Am. J. Physiol. **83**:578, 1928.

The bile-expelling mechanism of the guinea-pig was studied anatomically and physiologically on animals anesthetized by barbital, ether or a local anesthetic, or immediately after the sudden killing of the animal. A specialized mechanism was found, consisting of an ampulla lying on the duodenum, which underwent active contraction at the time of that of the duodenum. The simultaneous contraction of a strong sphincter prevented regurgitation into the common duct. Apparently, in the guinea-pig contraction of the gallbladder is slightly if at all concerned in causing the flow of bile. The close relation of the expelling mechanism to duodenal activity suggests the possibility of similar relations in other animals between the intramural portion of the common duct and duodenal peristalsis.

H. E. Eggers.

A Dietary Deficiency Disease in Dogs. F. P. Underhill and L. B. Mendel, Am. J. Physiol. **83**:589, 1928.

The pathologic change in dogs suffering from the deficiency disease described by Chittenden and Underhill in 1917 was found to be localized in the alimentary canal and most pronounced in the buccal cavity, taking the form of acute fibrinopurulent stomatitis, pharyngitis and ileocolitis. As regards its cause, it did not result from lack of inorganic salts in the diet; high nitrogen intake, either in the form of meat or legumes, did not prevent its onset, although this might be delayed; yeast possibly prolonged life, but had no curative effect. The protective factor was found present in fresh pig's liver and particularly in butter fat, in which it varied with the freshness and content in coloring matter. Egg yolk also contained the effective factor, though to a less degree than butter fat. Boiled unpeeled carrots were even more effective than butter, and the potent agent in these could be extracted by lard. The factor was lacking in cod liver oil and appeared to be associated with the carotinoid pigments. This view was confirmed by the fact that crystallized carotin in relatively small doses was effective as a cure.

H. E. Eggers.

THE BASAL METABOLISM IN SIMPLE AND CYSTIC ADENOMATOUS GOITER IN RELATION TO THYROIDECTOMY. GIOVANNI CALISSANO, Arch. per le sc. med. **49**:731, 1927.

In a person with slight hyperthyroidism the basal metabolism is increased, and several months following thyroidectomy, with an increase in weight and an amelioration of the clinical symptoms, a marked lowering of the basal metabolism occurs.

The basal metabolism is slightly above the normal in a person affected with a circumscribed adenomatous goiter. Following a thyroidectomy, it is lowered slightly to remain within the physiologic limits.

In a person affected with a cystic goiter, the basal metabolic rate is lower than normal and is increased after the operation.

The observed phenomena relating to exophthalmic and adenomatous goiters are in accord with those of other investigators. In the exophthalmic form, there is an excessive activity of the gland, whereas, in the simple adenomatous goiter a lowered secretion is present. In cystic goiter there is a disturbance in the functional activity of the gland followed by a lowering of the metabolic rate. This disturbance is improved by the removal of the cause.

BASAL METABOLISM IN PULMONARY TUBERCULOSIS. ANTHONY and H. L. KOWITZ, Beitr. z. Klin. d. Tuberk. **68**:18, 1928.

Fifty-three patients were examined once and twenty-six repeatedly at weekly intervals. It was found that the basal metabolic rate is frequently increased in persons with pulmonary tuberculosis, particularly in the presence of fever. There is no relation between the amount of increase and the type or extent of process. Patients who did not show any improvement or whose condition grew worse more frequently had a permanent increase in their metabolic rate. The intoxication cannot be the cause of the increased metabolism, since patients with severe toxemia were found sometimes to have normal rates. Patients with stationary lesions, but with elevated metabolic rates, are more likely to develop exacerbations after discharge from the hospital than similar patients with normal rates. Tuberculous patients frequently have a low respiratory quotient in spite of an increased metabolic rate. This suggests the possibility that after depletion of glycogen storage, the fat is metabolized.

MAX PINNER.

"MUSCLE WORK" AND INSULIN REQUIREMENT IN DIABETES. A. GERL and A. HOFMANN, Klin. Wchnschr. **7**:59, 1928.

A comparison of the blood sugar curves of three diabetic patients while at rest with those of a patient exercising shows that the units of insulin required by a diabetic patient are decreased when the patient does "muscle work." The author explains this by assuming that all cells of the body are capable of producing insulin.

R. BRENNWASSER.

UTILIZATION OF DI-HYDROXYACETONES BY DIABETIC PATIENTS. M. GROSSMANN and ST. POLLAK, Klin. Wchnschr. **7**:211, 1928.

This substance is rapidly assimilated and oxidized by diabetic patients and healthy adults. It influences the sensitive carbohydrate metabolism of the diabetic person considerably less than the same amount of dextrose. In diabetic patients after a temporary increase, the hyperglycemia and acidoses are diminished. With insulin, it is of value in combating comatose and precomatose conditions.

AUTHORS' SUMMARY.

RECURRENCE OF HEMOLYTIC ATTACKS FOLLOWING SPLENECTOMY FOR HEMOLYTIC ICTERUS. O. ROTH, Folia Haemat. **35**:1, 1927.

Roth explains the recurrence of hemorrhages following splenectomy on the basis that the functions of the removed spleen are taken up by the lymph nodes.

In a case studied by him, the removal of the spleen was followed by a vicarious enlargement of the mesenteric, hilum and paratracheal lymphatic glands. The possibility of the presence of an accessory spleen was excluded in this case.

B. M. FRIED.

THE INFLUENCE OF ARSENIC AND IRON ON THE VOLUME AND ON OTHER PROPERTIES OF THE BLOOD. GYÖZÖ PETRÁNYI, Folia. Haemat. **35**:19, 1927.

Arsenic and iron lead to an absolute increase of the circulating blood and particularly to the increase in its cellular elements. The diameter of the newly built cells is smaller and their color index is higher than usual. Petrányi found that the resistance of individual blood corpuscles is in direct proportion to the body weight. He could not find a relationship between the H-ion concentration and the viscosity of the blood.

B. M. FRIED.

THE OCCURRENCE OF POIKILOCYTOSIS IN DIFFERENT DISEASES. E. S. KANELLIS, Folia Haemat. **35**:65, 1927.

Kanellis found poikilocytosis in cases of secondary anemia following different diseases. In his experience, poikilocytosis was frequently accompanied by anisocytosis. The condition does not depend on the amount of hemoglobin or on the erythrocytic count. It can be produced by heating and to some extent by mixing blood from healthy persons with lecithin and cholesterin, which are normally present in human blood. Poikilocytosis was not observed in blood mixed with different solutions of sodium chloride. Kanellis stated that this anomaly of the blood is not only the result of some disturbance in the bone marrow, as thought by Arneth, but is apparently connected also with some kind of a pathologic phenomenon present in the circulating blood.

B. M. FRIED.

Pathologic Anatomy

CHRONIC SUBDURAL HAEMATOMA. F. C. GRANT, Ann. Surg. **86**:485, 1927.

Since Putnam and Cushing's article on this subject, several writers have drawn attention to the frequency of the condition. Grant reports three cases of chronic subdural hematoma developing subsequent to slight cranial trauma.

N. ENZER.

MALIGNANT DISEASE OF THE THYROID GLAND. E. M. EBERTS and R. R. FITZGERALD, Ann. Surg. **86**:515, 1927.

This article is an excellent summary of the clinical and pathologic aspects in malignant tumors of the thyroid. In all, 1,876 cases are reviewed. The bibliography includes 80 references.

N. ENZER.

THE PATHOLOGY OF CHARCOT JOINTS. W. J. POTTS, Ann. Surg. **86**:596, 1927.

Two conditions must be present to develop Charcot's joints — a change in the sensory nerves of the joint and trauma to the joint. Thus the condition occurs in tabes, syringomyelia, traumatic lesions of the cord, transverse myelitis and other conditions. Experimentally, section of the peripheral sensory nerves plus trauma produced typical changes in the joint. Such changes have not been definitely established in man. The combination of these two factors allows for repeated trauma to the joints with the resulting destruction and erosion of bone leading later to repair by sclerosis and excessive bone formation.

Six cases are described illustrating various stages in the process. The hypertrophic osteo-arthritis is the more common manifestation, but atrophy of

disuse occurs. The intra-articular changes are those of destruction of cartilage and sclerosis of the exposed bone. In some areas, the cartilage and synovia became thickened and fibrosed. Excessive connective tissue proliferation forms intra-articular villi.

N. ENZER.

GAUCHER'S DISEASE. H. E. SANTEE, Ann. Surg. **86**:707, 1927.

This disease is reported in two brothers.

N. ENZER.

SACRO-COCCYGEAL CHORDOMA. B. KWARTIN and J. D. STEWART, Ann. Surg. **86**:771, 1927.

A report of a case of sacrococcygeal chordoma and a description of the specimen is given. The tumor has not recurred in the three years since its removal.

N. ENZER.

OBTURATOR HERNIA. C. F. HORINE, Ann. Surg. **86**:776, 1927.

This article is valuable for its bibliography.

N. ENZER.

ADENOMA OF THE HYPOPHYSIS WITHOUT ACROMEGALY, HYPOPITUITARISM OR VISUAL DISTURBANCES TERMINATING IN SUDDEN DEATH. ESMOND R. LONG, Arch. Neurol. & Psychiat. **18**:576, 1927.

A chromophobe cell adenoma of the hypophysis was found in a man ,aged 37, who came to work one morning in apparently normal health and who suddenly became dizzy and vomited and a few minutes later became comatose. He became cyanotic and died four hours after the attack of dizziness in the morning. Postmortem examination showed a tumor of the hypophysis, extensive fibroplastic pleural and lymphnodal tuberculosis being the outstanding abnormalities. The tumor mass projected 2.5 cm. from the base of the brain and replaced the hypophysis. It was lobulated and measured 4 by 3 cm. in its horizontal aspect. Microscopically, the bulk of the tumor was found to consist of columns or alveoli of epithelial cells of uniform size with deep staining nuclei and a moderate amount of cytoplasm separated by a stroma rich in thin-walled blood sinuses. The growth was adenomatous and the edge of the tumor mass contained compressed rows of cells representing remains of the original anterior lobe of the hypophysis. Ethyl violet-orange G. preparations showed the cells of the tumor to be uniformly of the chromophobe type.

T. T. STONE.

TUMORS OF THE PINEAL GLAND. KEENE O. HALDEMAN, Arch. Neurol. & Psychiat. **18**:724, 1927.

The author reported two cases of glioma of the pineal gland. Clinically, the most important aids in localizing such tumors are disturbances of eye movements. The tumors were described as gliomas of the pineal gland and one was associated with a large syringomyelic cavity in the spinal cord. He further summarized 113 cases of tumore of pineal gland and found the following incidence: sarcoma, 24; teratoma, 22; cyst, 14; glioma, 11; pinrsloms, 10; hyperplasia, 4; carcinoma, 4; adenoma, 4; psammoma, 2; and unclassified, 18. Out of 102 cases, 78 occurred in males and 24 in females. He was unable to draw any conclusions regarding the function and significance of this gland due to the contradictory results obtained in the experimental work on pineal gland feeding of animals and of defective children and on the destruction of the pineal gland in animals.

T. T. STONE.

ON THE GLANDULAR ELEMENTS IN THE POSTERIOR LOBE OF THE HUMAN HYPOPHYSIS. DEAN LEWIS and F. C. LEE, Bull. Johns Hopkins Hosp. **41**:241, 1927.

From a study of complete serial sections of thirty human hypophysis varying in age from birth to 73 years, as well as from the examination of many other individual sections, glandular tissue was found at all ages in the posterior lobe. In the new-born and in very young children tubuloracemose glands, communicating with the hypophyseal cleft, were frequently present to a marked degree until the fourth year. After that time only occasional tubular glands were seen. These tubular glands were usually situated in the anterior and lateral portions of the posterior lobe, as well as at the point of attachment of the hypophyseal stalk. Colloid material was seen in these gland cells which stained like the substance found in the duct, cyst or cleft into which the gland emptied. The other chief glandular element was a basophilic cell which resembled the basophil of the anterior lobe in many particulars. This cell was present at all ages, but became more numerous, and invaded the posterior lobe progressively with increasing age. Masses of these basophilic cells were sometimes found high up along the hypophyseal stalk and near the dorsum sellae. Individual basophilic cells were frequently seen as part of the lining of ducts and cysts. There was no constancy in age incidence or position for any of these glandular elements which deserve to be included under the term pars intermedia.

AUTHORS' SUMMARY.

CEREBRAL CICATRIX: THE REACTION OF NEUROGLIA AND MICROGLIA TO BRAIN WOUNDS. P. DEL RIO-HORTEGA and WILDER PENFIELD, Bull. Johns Hopkins Hosp. **41**:278, 1927.

The formation of a simple cicatrix in the brain presents the following stages: The first cellular change is observed in microglia cells which begin their phagocytic activity early and continue it for a long period. Later, the neuroglia astrocytes about the wound become swollen and those closest to the area of destruction or to obliterated vessels undergo clasmatodendrosis. Rapid amitotic division of the other astrocytes follows and the cells then become fibrous and arrange themselves typically in a radial fashion about the wound. A connective tissue core forms at the center, connective tissue collagen fibrils are laid down and the wound contracts. In stabs in which connective tissue core is not present, there is no tendency for a radial arrangement of the astrocytes and no evidence of contraction. Compound granular corpuscles were numerous in the wounds. Transitions could be seen from microglia to these cells, but evidence was not found of astrocytes becoming mobile or developing into the foregoing cells. When products of degeneration had disappeared from the wound, microglia in its complicated spiderlike form appeared in the scar.

AUTHORS' SUMMARY.

TUBULAR NEPHRITIS (NEPHROSIS) IN CHILDREN AND ITS RELATIONSHIP TO OTHER FORMS OF NEPHRITIS. WILBUR C. DAVISON and ROBERT SALINGER, Bull. Johns Hopkins Hosp. **41**:329, 1927.

Of twenty-six children diagnosed as having tubular nephritis, definite information was secured in regard to twenty, and of these six are well, six are dead, and in eight the disease is still active. It is concluded that tubular nephritis is a definite disease of unknown cause, but that the prognosis is perhaps better than has been indicated by other reports. The term, tubular nephritis, is regarded as preferable to nephrosis. The presence or absence of hematuria and edema is the most satisfactory criterion at present for classifying nephritis in children into glomerular, tubular and interstitial.

STUDIES IN EXPERIMENTAL EXTRACORPOREAL THROMBOSIS. TAKUJI SHIONOYA, J. Exper. Med. **46**:957 and 963, 1927.

The effects of environmental temperature on thrombosis in circulating blood were tested in the extracorporeal loop by the method previously described. Cold (from 7 to 15 C) about the collodion tube retards the clotting of circulating blood. Obstruction of the arterial cannula occurs after from fifteen to twenty-five minutes. Heat (40 and 55 C.) tends to hasten clotting; obstruction by red clot takes place after from four to six minutes and from two to four minutes, respectively. In the latter case, no characteristic thrombus structure may be seen. These results were what might be expected. The formation of white thrombi occurs even under the influence of cold, and they continue to form and grow as long as the circulation continues. When the carotid artery is partially occluded and the blood stream slowed, after the injection of the anticoagulent, the blood has a tendency to form red thrombi on the foreign surface of the vascular loop. The thrombi are deposited chiefly in the arterial half of the apparatus, especially at the bottom of the arterial end of the collodion tube, just as in the case of Aschoff's sand experiments. In spite of incoagulability of heparinized blood, red clots, with interwoven fibrin bands, are found. Also tiny white thrombi may form in other parts of the collodion tube.

The effect of complete obstruction of the carotid artery and jugular vein on thrombus formation was studied after the use of anticoagulant. When the carotid artery is obstructed the formation of white thrombi is negligible and sedimentation of erythrocytes and deposition of fibrin appear throughout the apparatus; then the blood, at a standstill, clots slowly. When the jugular vein is obstructed, dislodgment of platelet thrombi probably results from the pulsating movement, and sedimentation of erythrocytes follows, forming mixed thrombi. The dislodged white thrombi tend to gather in the bottom of the tubes of the widest caliber, especially in the collodion tube.

Distilled water dialyzes through the collodion tube and causes hemolysis. Clotting of the hemolyzed blood in the collodion tube occurs later. Bile salts accelerate the appearance and development of white thrombi in the heparinized animal. The masses of white thrombi are loose, soft, fragile and easily broken into clumps of platelets. They are poor in fibrin or the fibrin is abnormal, since they have less retractility than those obtained from the use of physiologic sodium chloride solution or calcium chloride or serum. Despite the increase in number and size of white thrombi, normal clotting does not occur. When the collodion tube is surrounded by 1 or 2 per cent d-glucose solution, tiny and numerous white thrombi appear as radiating figures. The masses of white thrombi are rather loose and fragile. The clotting time of the heparinized blood does not appear to be shortened. When a 1 to 2 per cent solution of calcium chloride is used as the dialyzing fluid outside the collodion tube, or when it is injected into the circulation, the formation of white thrombi is accelerated. They grow rapidly. In spite of the action of heparin, the white thrombi formed are not so fragile as when bile salts are placed outside of the collodion tube. Fibrin seems to form easily. Obstruction of venous cannula takes place speedily, and if the clots in the cannula are not removed, the white thrombi in the collodion tube remain small and become red by sedimentation of red cells. Intravenous use of 10 per cent solution of magnesium sulphate without heparin retards the coagulation of circulating blood and permits the blood to flow through the extracorporeal loop from three to four times as long as normal. The formation of white thrombi, as well as red, is retarded. Magnesium sulphate (1 per cent) in physiologic sodium chloride solution placed outside the collodion tube markedly retards the formation of white and red thrombi in the heparinized animal. Magnesium sulphate (10 per cent), 50 mg. for each kilogram of body weight each hour, administered intravascularly in the heparinized animal, definitely prevents the first stages of thrombosis, and consequently prevents clotting. It is possible, by the combined use of adequate amounts of magnesium sulphate and of heparin intravenously, to prevent all stages of thrombus formation for from one to three hours.

AUTHOR'S SUMMARY.

THE MECHANISM OF THE INFLAMMATORY PROCESS. HAROLD A. ABRAMSON, J. Exper. Med. **46**:987 and 1002, 1927.

The velocity of cataphoretic migration of blood cells in plasma and serum is proportional to the potential drop applied. The cataphoretic velocity of red cells, polymorphonuclear leukocytes, small lymphocytes and large lymphocytes is described for serum and plasma. The relation between the electrokinetic potential of white blood cells and the differences of potential probably existing in injured tissues are correlated quantitatively. This correlation suggests that migration of leukocytes to a point of injury is, in part, dependent on the electromotive forces at play in the tissues.

Observations on the behavior of a frog leukocyte in vivo have led to the conclusion that an adhesive force of at least 10^{-3} dynes may be offered by one pseudopod. This adhesive force of one pseudopod, is of the order of magnitude sufficient to cause leukocyte arrest previous to emigration through the capillary wall.

AUTHOR'S SUMMARY.

THE SIGNIFICANCE OF HEMAL NODES. H. E. JORDAN, J. Morphol. **44**:89, 1927.

The investigation is based on hemal nodes of dog, man and sheep. The material can be arranged in a regressive series leading from a typical lymph node, except for the occurrence of blood in parenchyma and sinuses, to a lymphoid structure at a late stage of involution. These structures uniformly lack lymphatics. There is no evidence of direct luminal connection between the blood-vascular supply and the sinuses. The observation that certain cervical and subcutaneous lymph nodes of the rabbit undergo a myeloid metaplasia following atrophy and disjunction of their lymphatics is used as an explanatory key of hemal nodes. According to our view, hemal nodes represent stages in the involution of transient lymph nodes. Disjunction of the lymphatics leaves the sinuses filled with entrapped lymphocytes. These differentiate into erythrocytes. These red blood cells may disintegrate and pass into solution or be removed either by giant cells or mononuclear phagocytes. Late stages in this process are represented by small irregular masses of lymphocytes, with wide sinuses practically free of blood.

AUTHOR'S SUMMARY.

FAMILIAR FORM OF ENCEPHALITIS PERIAXIALIS DIFFUSA. ARMANDO FERRARO, J. Nerv. & Ment. Dis. **66**:329, 1927.

The author describes the brains of two brothers and a sister who constituted the only children of the family.

Myelin Sheath: The white matter is the seat of a pronounced and diffuse demyelination, noticeable also to the naked eye. Globoid cells appear in areas where myelin is intact or nearly so. Myelin bodies are those that result from breaking down of the myelin. Both the globoid cells and myelin bodies are seen numerous around the blood vessels and even in the perivascular spaces.

Nerve Fibers: The nerve fibers show everywhere evident signs of involvement. The pronounced lesions of the nerve fibers, in general, occur in those areas showing highest damage of the myelin sheaths.

Neuroglia: The whole white matter appears to be the seat of a diffuse gliosis. The intensity of the gliosis varies from area to area. Gliosis of the fibrous type is seen in the inner layers of the cortex while a gliosis of the protoplasmic and fibrous type is seen in the outer layer of lamina molecularis.

Waste Products: Large numbers of globoid cells with fat granules (gitter cells) are present throughout the section.

Ferraro concluded that a large amount of the mobile gliogenous cells in his cases represent a degenerative form of the neuroglia cells, and that possibly a primary deficiency of the neuroglia cells is at the base of the failure in the elaboration of the abbau products; also that the process of abbau is performed by the mobile type of neuroglia cells. The clinical diagnosis in all three cases was multiple sclerosis.

T. T. STONE.

AMYOTROPHIC SYPHILITIC MENINGOMYELITIS: REPORT OF TWO CASES WITH ARGYLL-ROBERTSON PUPILS. THEODORE T. STONE, J. Nerv. & Ment. Dis. **66**:595, 1927.

Two cases of muscular atrophy are reported in a woman and a man who showed Argyll Robertson pupils. The literature of this condition is reviewed. A summary of the changes follows: chronic leptomeningitis throughout the whole length of the cord and medulla; severe ependymitis in the fourth ventricle; intense glial reaction toward both surfaces of the brain stem; intense degeneration of the white matter around the margin of the cord (marginal degeneration); degeneration of the cells of the anterior horn and of the cells of Clarke's column, almost absolute in the cervical enlargement, much less but still definite throughout the remainder of the cord. The degeneration of the more central white matter is less marked, the columns of Burdach being the least affected. This tract degeneration is most pronounced in the middle and cervical enlargement of the cord. There is a moderate degree of arteritis of the meningeal and intraspinal arteries, affecting chiefly the intimal and adventitial coats of the vessels. Small vessels within the cord are increased in number. Throughout the cord and meninges there is a moderate amount of perivascular infiltration with lymphocytes. Because of these changes it is concluded that the disease was syphilitic in origin.

AUTHOR'S SUMMARY.

HEALED TUBERCULOMA OF THE CEREBELLUM. M. J. STEWART, J. Path. & Bact. **30**:577, 1927.

Cases of healed and calcified tuberculoma such as the one here described afford a definite anatomic basis for the well-known clinical fact of recovery from symptoms of cerebral tumor, although it is not suggested that more than an occasional case of this kind can be so accounted for. As in cases of tuberculous meningitis, the patients who recover completely are so few that they must be allowed to carry very little weight in estimating the prognosis in a given case.

AUTHOR'S SUMMARY.

LARGE CALCIFIED TUBERCULOMA OF CEREBRUM WITH INDEPENDENT TERMINAL CEREBRAL HAEMORRHAGE. RALPH P. SMITH, J. Path. & Bact. **30**:583, 1927.

Whatever the exact nature of the calcified deposit may be, it seems to have developed after the illness at 4½ years of age, as the patient never subsequently suffered from any severe illness, and it appears to have remained present throughout the whole lifetime of the patient, being discovered only at postmortem examination.

AUTHOR'S SUMMARY.

EFFECTS OF COAL DUST UPON THE SILICOTIC LUNG. S. L. CUMMINS, J. Path. & Bact. **30**:615, 1927.

A case is described in which it appears that through blocking of the lymph vessels of the lung from silicosis, coal dust accumulated to the extent that it acted like a foreign body and lead to extensive fibrous changes.

A HYPERNEPHROMA OF ATYPICAL STRUCTURE. JOHN GRAY, J. Path. & Bact. **30**:641, 1927.

A renal tumor containing tissue of a papilliferous cystadenomatous type and also tissue of a typical hypernephroma type showed on examination such gradual transition from the one type to the other as to suggest that tumors of the kidney of the two types may sometimes have an identical origin. While the portions of typical hypernephroma showed considerable resemblance to the suprarenal cortex, the presence of portions in which a definite arrangement

into circular tubules like renal tubules suggests a renal rather than an suprarenal origin for at least this particular "hypernephroma."

AUTHOR'S SUMMARY.

THE PRODUCTION OF EXPERIMENTAL ATHEROMA WITH CHOLESTEROL. R. W. SCARFF, J. Path. & Bact. **30**:647, 1927.

Atheromatous lesions can easily be obtained in rabbits by the addition of cholesterol to a normal diet. Some months after the feeding is discontinued the lesion assumes a form which, both macroscopically and microscopically, bears a strong resemblance to human atheroma. In a limited series of experiments the increase in blood cholesterol has not been accompanied by any alteration in blood pressure.

AUTHOR'S SUMMARY.

REGENERATION OF THE PANCREAS. G. R. CAMERON, J. Path. & Bact. **30**:713, 1927.

In the guinea-pig excision of part of the pancreas is probably followed by regeneration of acinar and islet tissue. Regeneration is inhibited by giving insulin or pituitrin. Both insulin and pituitary cause hypertrophy of the pancreas, and pituitary produces an increase in the relative amount of islets.

AUTHOR'S SUMMARY.

CONGENITAL AND ACQUIRED ABNORMALITIES OF THE PULMONARY ARTERY. R. C. CLARKE, C. F. COOMBS and G. HADFIELD, Quart. J. Med. **21**:51, 1927.

The object of this report is to confirm the view that there are syphilitic and nonsyphilitic abnormalities of the pulmonary artery and to advance the idea of a probable inherited etiologic factor in connection with the latter. Dyspnea and cyanosis were prominent symptoms in the five patients who eventually came to autopsy. The syphilitic type was represented in a woman, aged 39, who had shortness of breath and cough for three years before death, and whose body was the seat of a generalized syphilitic arteritis, manifested in the lungs as an obliterating endarteritis accompanied by a gross perivascular pulmonary fibrosis. The primary, nonsyphilitic type of pulmonary sclerosis occurred in a woman, aged 22. The condition was most pronounced in arteries from 7 to 3 mm. in diameter, as acellular, nodular intimal thickenings devoid of inflammatory reaction. A congenitally wide pulmonary artery, twice the size of the aorta, was found in a girl, aged 10 months, dying of bronchopneumonia; and an interventricular septal defect, an anatomically patent foramen ovale and a generalized dilatation of the pulmonary artery and its branches were seen in a boy, aged 6 months, who died suddenly. A girl, aged 6 years, had marked atheromatous changes in her pulmonary arterial system, and her family history was carefully investigated. The father died at the age of 47, from rheumatic heart disease; one sister died at the age of 3½ years of bronchopneumonia; another died at the age of 1½ years after bronchitis; one brother died at the age of 8 months of bronchitis; another drowned at the age of 20 months. A 4 year old sister had had dyspnea and cyanosis for two years and had been closely observed since the onset of the symptoms.

GEORGE RUKSTINAT.

IRON CONTENT OF THE TISSUES IN HAEMOCHROMATOSIS WITH SPECIAL REFERENCE TO THE BRAIN. J. H. SHELDON, Quart. J. Med. **21**:123 (Oct.) 1927.

A heavy drinker, aged 46, developed a left-sided hemiplegia and five years later, a bluish-bronze pigmentation of the soft palate and skin of the legs and marked drowsiness. A 50 Gm. dextrose tolerance test revealed an imperfect storage mechanism, but no frank diabetes mellitus. At autopsy, the liver was markedly cirrhotic, the pancreas fibrous and pigmented. Iron-containing pigment

was demonstrable in practically all tissues, and the percentages of iron in the more outstanding departures from normal are herewith tabulated.

	Present Case, Per Cent Iron	Normal, Per Cent Iron
Liver	3.94	0.08 to 0.18
Pancreas	0.58	0.105
Spleen	0.79	0.17
Lymph glands	....	0.15
(1) Near pancreas	14.10	....
(2) Mesenteric	8.55	....
(3) Iliac	7.24	....
Thyroid	0.40	0.07
Cerebellum (lateral lobe)	0.075	0.060
Deiter's nucleus	0.281	0.341
Pons	0.176	0.077
Putamen	0.483	0.183
Thoracic cord	0.329	0.089
Basal ganglia	0.174	0.057
Blood	0.050	0.054

The two outstanding subnormal iron percentages are in the blood and Deiter's nucleus. The former agrees with previous observations and supports the view that the essential feature of hemochromatosis is an abnormal avidity of the tissues for iron. In the absence of diabetes, the drowsiness is attributed to the hemochromatosis.

GEORGE RUKSTINAT.

CALCIUM METABOLISM IN THE BRAIN. I. BERTRAND and R. ALTSCHUL, Rev. neurol. **34**:241, 1927.

In this histologic study the authors review the subject of calcification in the central nervous system. Every part of the brain may show calcification. In the arachnoid there is scale formation, while in the dura a typical form of osteogenesis takes place. It is an interesting fact that the tentorium in cats and dogs, and the falx cerebri in certain submammalian species are found to be normally ossified. The tendency of the human dura toward ossification may, therefore, present the phenomenon of a reversal to an ancestral disposition. Calcium deposits are frequent in the choroid plexus in the course of chronic cerebral diseases. In cases of epidemic encephalitis, especially in its prolonged subchronic variety, a calcinosis of the intracerebral arterioles is frequently observed. Calcium deposits are also found with considerable frequency in cases of infantile encephalopathy. Among the tumors, it is especially the fibroendothelioma and the psammoma which show a tendency toward calcification. In the pineal gland, the calcium deposits are a regular occurrence after the age of 7 years.

A. LOW.

METASTATIC NEOPLASMS IN THE SPLEEN. NOEL ORLANDI, Tumori **13**:545, 1927.

Orlandi has studied the occurrence of primary and metastatic tumors of the spleen and finds that although the spleen is an organ less subject to invasion by neoplasms, the occurrence of them is not altogether exceptional. He observed a peculiar unexplained atrophy of the spleen in patients with malignant tumors. While the spleen is rarely the seat of primary tumors, it contains metastatic growths fairly frequently. It differs in this way from the pancreas, in which primary tumors are relatively frequent and metastases rare.

W. OPHÜLS.

REACTIONS OF THE KUPFFER CELLS OF THE LIVER TO INJURY. B. MALYSCHEW, Beitr. z. path. Anat. u. z. allg. Pathol. **78**:1, 1927.

The purpose of Malyschew's work was an investigation of the differentiation potentialities of the Kupffer cells of the liver. The experimental procedure consisted of piercing the liver tissue of rabbits with a red hot needle, the tissue

being examined at survival periods of from one-half hour to forty days. In three animals the same procedure was carried out after vital staining with trypan-blue, the animals being allowed to live from one-half hour to two days after the experimental injury. The Kupffer cells are part of the reticulo-endothelial system and possess the potentialities of the cells of this system. Under normal conditions they are the least differentiated cellular elements within the liver but at the same time they are the most resistant to injury and the most active in regard to their potentialities. In the reaction zone about the area of necrosis caused by the experimental procedure used, the Kupffer cells enlarge, become detached and within the vascular lumen become transformed into primitive hemocytoblasts, which form myelocytes and megakaryocytes. Previous vital staining with trypan-blue hinders myelopoiesis. Some of the reacting Kupffer cells become ameboid and wander into the extravascular tissues, where they form macrophages, fibroblasts and capillaries. Lymphocytes are formed both within and outside the vessels. The epithelium of the bile ducts also proliferated actively and formed new ducts.

O. T. SCHULTZ.

LEUKOCYTIC INFILTRATION OF THE PLACENTA. K. IKEDA, Beitr. z. path. Anat. u. z. allg. Pathol. **78**:16, 1927.

Leukocytic infiltration of the placenta is seen not infrequently. According to Ikeda it occurs in normal pregnancies and is especially frequent after stillbirth or forceps delivery. Its presence does not bear any relation to the duration of labor or to the strength of the uterine contractions. It occurs more frequently in that portion of the placenta surrounding the insertion of the cord than in more peripheral portions, or than in the free chorionic membrane. It may surround the umbilical vessels, and in the placenta itself is localized just beneath the chorionic membrane or at the side of the chorionic vessels nearest the amniotic cavity. In opposition to the conception of Ricker, who considers leukocytic emigration to be part of the neurovascular phenomenon of inflammation, Ikeda could detect no nerve fibers in the placenta nor any vascular reactions by means of pharmacologic experimentation which would indicate the presence of nerve control of the placental and umbilical vessels. He concludes that the leukocytic infiltration observed by him is the result of chemical and physical factors present in the amniotic fluid, which act directly on the vessels of the cord and villi and those just beneath the chorionic membrane.

O. T. SCHULTZ.

RADIOLOGIC STUDY OF STRUCTURE OF GALLSTONES. E. LOEFFLER, Beitr. z. path. Anat. u. z. allg. Pathol. **78**:44, 1927.

Although gallstones can only rarely be demonstrated in the living patient by means of the roentgen ray, the author claims that the study of calculi outside the body by means of very soft rays yields important information in regard to the structure of the stones. The roentgenographic observations, which were controlled by sections from 20 to 30 microns thick through the center of the stone, confirmed the views of Aschoff and Bacmeister in regard to the structure and genesis of gallstones.

O. T. SCHULTZ.

CALCIUM GOUT. VIOLET STAUB, Beitr. z. path. Anat. u. z. allg. Pathol. **78**:67, 1927.

M. B. Schmidt proposed the name calcium gout for a condition in which there is widespread calcification of soft tissues without destructive bone changes, as opposed to the process termed calcium metastasis by Virchow, in which the calcification is associated with bone changes and usually with nephritis. Because of the deposition of calcium phosphate and carbonate in the skin and about the joints, especially of the phalanges, the similarity to

gout may be striking. In the case studied by Staub, a youth, aged 18, the calcium of the blood was increased but calcium excretion in the feces and urine was normal. Blood phosphorus was also higher than normal, phosphorus excretion being only slightly increased. Hypercalcemia and hyperphosphatemia were therefore considered to be important factors in the calcium phosphate deposition characteristic of the disease. Since the higher blood calcium content cannot be ascribed to increased withdrawal from the bones or to deficient excretion, the disease is considered an endogenous disturbance of intermediary calcium and phosphorus metabolism, possibly on an endocrine basis.

O. T. Schultz.

Experimental Fat Embolism. T. Shinkai, Beitr. z. path. Anat. u. z. allg. Pathol. **78**:109, 1927.

In an experimental inquiry into the reason for the greater involvement of the lungs in fat embolism, Shinkai found that when olive oil was injected into a vein in the ear of the rabbit the capillaries of the lungs contained a greater amount of the oil than the vessels of any other organ or tissue. If the oil was injected into the left side of the heart, the amount of material in the other organs was almost as great as in the lung, but it remained longer in the lung than elsewhere. When pieces of lung were transplanted into the kidney, liver or spleen, and the injection made after fifteen days, such transplants shared with the normally situated lung, the latter's predilection as a site for fat embolism. Factors invoked to explain the pulmonary localization are the high viscosity of fat on the one hand, and on the other, the tortuosity and distensibility of the capillaries of the lung, the low pressure in the pulmonary artery, and the fact that the pulmonary circulation constitutes the first filter for fat which enters the venous circulation. O. T. Schultz.

Arteriosclerotic Vascular Rupture and Cerebral Hemorrhage. A. Rühl, Beitr. z. path. Anat. u. z. allg. Pathol. **78**:160, 1927.

As the result of his own examination of the brains in cases of cerebral hemorrhage and of softening, Rühl disagrees with Westphal, who claimed that the primary factor in cerebral hemorrhage is vascular spasm and that this is followed successively by anemia, damage to the brain and vessels and finally hemorrhage. Rühl holds atherosclerosis to be the fundamental process. This is of such a character that it leads to atheromatous degeneration of the vessel wall, which ruptures as the result of the associated hypertension. The destruction of brain tissue by the hemorrhage leads to secondary rupture of neighboring intact vessels, and to the formation of the so-called small aneurysms of the cerebral vessels. Such aneurysms are intramural or extramural hematomas of weakened portions of the vessel wall.

O. T. Schultz.

Cysts of the Seminal Vesicle. H. Francke, Centralbl. f. allg. Pathol. u. path. Anat. **41**:145, 1927.

In a man, aged 69, dying of a spontaneous intracerebral hemorrhage, the following observations were made post mortem: A cylindric mass 12 by 5 cm. occupied the right side of the small pelvis, and was connected to the pelvic wall by loose fibrous adhesions laterally and posteriorly, covered with peritoneum elsewhere and firmly adherent to the pelvic floor. Its wall was firm, from 1 to 3 mm. thick, and its lumen was divided into three nearly equal chambers by slightly oblique partitions 2 mm. thick. An opening the size of a pencil in each partition allowed free intercommunication between the chambers. The lowermost compartment opened into a duct, funnel-shaped at each end, constricted at its middle and describing an anterior right angle before opening into the colliculus seminalis. The fluid in the chambers was watery and contained spermatozoa. The cyst was regarded as of congenital origin.

George Rukstinat.

DEMONSTRABLE IRON IN THE LIVER AND SPLEEN OF FETUSES AND NEW-BORN BABES. P. BOECKER, Centralbl. f. allg. Pathol. u. path. Anat. **41**:193, 1927.

From a review of the literature, the author concludes that examination of the liver and spleen usually discloses the presence of iron; and fluctuations in the amount of iron during intra-uterine and postuterine life seem to follow the same physiologic rules in humans and animals. In all, he examined sixty persons, whose ages were between 1 month (intra-uterine life) and 48 hours (postuterine life) at full term. Syphilitic patients were excluded. The Berlin blue and Hueck's modification of Turnbull's blue reaction were used as a means of studying the iron deposits. In the liver, the iron granules were found in the Kupffer's cells, liver cells, perivascular tissues and, at times, in the lymph spaces. In the spleen, the greatest deposits were in the sinus epithelium and perivascular tissues. Graphically represented there was a slow increase in iron in both organs during the first three months of intra-uterine life, when a rapid increase to three times this amount in the fifth and sixth months, a drop to a median position in the seventh and eighth months and again a rapid rise in the ninth and tenth months. It is suggested that these waves of iron deposition are related to the action of the liver, spleen and bone-marrow in the formation of blood.

GEORGE RUKSTINAT.

PATHOLOGIC ANATOMY OF THE LUNG IN WHOOPING COUGH. FRIEDRICH FEYRTER, Frankfurt Ztschr. f. Path. **35**:213, 1927.

In an epidemic of whooping cough the author studied 225 cases which came to autopsy. He found that the lungs early become involved in the course of whooping cough. Inflammation of the bronchial tree takes place early and remains permanently. These changes consist of mucopurulent endobronchitis and endobronchiolitis, high grade peribronchitis and peribronchiolitis. Bronchiolitis fibrinosa occurs often and may be followed by bronchiolitis obliterans. Bronchiectasia is common; bronchialstenosis may also be found. The peribronchitis explains the long duration and frequent exacerbations which occur in whooping cough and the peculiar sounds of the bronchial râles.

The disease of the greater bronchial tree is diffuse while severer forms of endobronchitis are unusual and come about through secondary infection. From the bronchiolitis and peribronchiolitis arises an interstitial pneumonia which remains as a small nodular peribronchial pneumonia. In many cases the interstitial inflammation passes through the alveoli causing the formation of exudate. The inflammation spreads frequently by the lymph vessels to produce other localized areas of peribronchiolar pneumonia. The areas of focal pneumonia may spread out over a limited area and become indurated or fill up the alveoli to the borders of the lobule and become chronic interstitial acinar or lobular pneumonia.

Croupous and also carnifying lobar pneumonia are not seen in cases of whooping cough. The exudate is mostly leukocytic, rarely fibrinous and then only in limited amount.

In chronic cases, vicarious emphysema is rarely seen. Changes in the pleura are in the form of fresh fibrinous pleuritis which is poor in cells; in chronic cases the pleurae are adherent. The vessels in the affected part of the lung in the chronic cases show hyperplasia of the elastic and collagen fibers in both the intima and media. In 32 cases of 225 there were evidences of tuberculosis.

E. M. HALL.

UNUSUAL METASTASES OF A SARCOMA WITH THE EXISTENCE OF TWO TUMORS. EBERHARD HAMMANN, Frankfurt Ztschr. f. Path. **35**:256, 1927.

The author reports the case of a butcher, aged 41, who had about twenty small nodules in the skin of the trunk and thighs. Excision of one of these nodules revealed what was considered to be a granulomatous inflammatory process involving the muscle. Syphilis with multiple gummas was considered. The Wassermann reactions of the blood and spinal fluid, however, were nega-

tive. The diagnosis was in doubt, but the condition was thought to be myositis nodosa. A month later the patient developed headache, cramps in the abdomen and pain in the sacral region. He died suddenly, apparently of heart failure. At autopsy, a spindle cell sarcoma was found in the thyroid gland with metastases in the striated muscle, heart, brain, lungs, kidneys, intestine and diaphragm. In addition to this, generalized sarcomatosis, a hypernephroma the size of an apple was found in the right kidney.

E. M. HALL.

A DERMOID OF THE FOURTH VENTRICLE OF THE BRAIN. DÉNES GÖRÖG, Frankfurt Ztschr. f. Path. **35**:265, 1927.

The author reports a case of a woman, aged 50, who became suddenly ill with severe headache, vomiting and dizziness, and died on the eighth day of her illness. At autopsy, a dermoid was found in the fourth ventricle of the brain. Examination revealed normal pupils but high grade bilateral ptosis. Nystagmus was present. All tendon reflexes were present and equal except the left knee jerk which was increased. Pathologic reflexes were present on both sides; abdominal reflexes were normal. There was no clonus or ataxia. The muscles were tonic, and passive movements were resisted. Movements of the facial muscles were weak, with partial paralysis of the right side of the mouth. Speech was soft, slow and dragging, yet understandable. Answers to questions were logical and clear. The patient slept a great deal but was easily awakened. Athetoid or choreiform movements were not present. There was a well marked stiffness of the neck, and passive movements of the head were painful. The Kernig sign was present bilaterally. The lumbar puncture revealed a clear spinal fluid with a pressure of 160 mm. Nonne-Apelt, Weichbrodt and Pandi reactions were negative. The cells were not increased and bacteria were not present. As stated, the patient died on the eighth day of her illness. At the autopsy, a tumor was found on the floor of the fourth ventricle of the brain. This mass was flat, broad, crumbly, pale yellow and about the size of a hazelnut. The surface was uneven and of a fatty appearance. Many light brown hairs were embedded within the mass. The growth covered the opening of the aqueduct of Sylvius and lay under the velum medullare posterius.

E. M. HALL.

HEMORRHAGES IN THE BRAIN IN LEUKEMIA. GERHARD ROSENKRANZ, Frankfurt Ztschr. f. Path. **35**:359, 1927.

The author reviews the literature and reports hemorrhages into the brain in two cases of leukemia. He believes that through changes in the condition of the blood in leukemia stasis and leukocytic thromboses occur in the smaller vessels, which in turn lead to bleeding by diapedesis through the undamaged vessels. A second origin for the hemorrhages is also noted in injury to the vessel wall due to marked fatty degeneration of the endothelium of the capillaries and precapillaries. The latter changes depend on nutritional congestion or on the presence of a circulating toxin in the blood or perhaps both.

Rosenkranz states that various cerebral symptoms in leukemia such as headaches, restlessness, vomiting and light paralyses may be due to cerebral hemorrhages, likewise, death may follow such an event.

E. M. HALL.

REGENERATION OF THE SPLEEN. BORIS BRANDSBURG, Ztschr. f. d. ges. exper. Med. **57**:145, 1927.

Bransburg reviews the contradictory literature on regeneration of the spleen. In his experiments dogs were used; the animals were killed after from five to ninety-eight days following the operation. It was found that after complete splenectomy new splenic tissue was not formed. After complete splenectomy and transplantation of a piece of spleen in the omentum, the transplant became necrotic and was resorbed. After transection of the spleen the individual pieces

did not enlarge; the wounds healed by scar tissue formation. After partial resection of the spleen the remaining pieces became enlarged, and microscopically, showed regeneration (hyperplasia of the pulp and of the follicles). After partial resection with associated transplantation in the omentum of portions of the spleen there usually occurred resorption of the transplant, but occasionally well defined growth. There was a marked loss of fat (subcutaneous, omentum, mesentery) in all splenectomized animals.

The second part of the paper deals with the reaction of the reticulo-endothelial system following complete or partial splenectomy. The latter operation was followed by well marked hyperplasia of the reticulo-endothelial cells, particularly in the liver and lymphnodes. After incomplete resection of the spleen, with subsequent regeneration of the organ, hyperplasia of the reticulo-endothelial system was not noted. The experimental facts appear to show a close relation between the function of the spleen and of the other parts of the reticulo-endothelial system.

BALDUIN LUCKE.

Pathologic Chemistry

MUSCLE HEMOGLOBIN IN HUMAN AUTOPSY MATERIAL. W. W. WOODRUFF and G. H. WHIPPLE, Am. J. Path. **4**:75, 1928.

A method is described for the quantitative analysis of the hemoglobin of the muscle in autopsy material. In twenty-three cases studied, values of from 550 to 1,120 mg. per hundred grams of muscle were found. The hemoglobin of the muscle was apparently only slightly influenced by fluctuations in the hemoglobin of the blood. The highest values were found in active young adults who died after a short illness. Low values were found in patients with chronic diseases and wasting illnesses. In every case in which there was an exceptionally low value there had been prolonged inactivity. It is concluded that in man, as in the dog, the concentration of the hemoglobin within the muscle fibers is determined more by muscular activity than by the level of hemoglobin in the blood.

AUTHORS' SUMMARY.

URINARY PROTEINS NOT ORIGINATING IN THE BLOOD. W. A. THOMAS, KARL W. SCHLEGEL and EDMUND ANDREWS, Arch. Int. Med. **41**:445, 1928.

Thomas, Schlegel and Andrews worked with catheterized specimens of urine from dogs which had been rendered uremic, and from other dogs after ether anesthesia. The urines were tested by the precipitin test against the serum of rabbits previously sensitized to dog blood proteins. Samples of urine taken early in the course of the experiments, with strong protein tests, were free from blood proteins.

H. R. FISHBACK.

ORIGIN OF URINARY PROTEINS. EDMUND ANDREWS and W. A. THOMAS, J. A. M. A. **90**:539, 1928.

The urinary proteins were studied in various forms of nephritis in dogs. By the precipitin test it was found that in the earliest stages the urinary proteins appeared to come from the liver and to be almost free from blood protein. In the later stages, blood proteins appeared in the urine also.

HYPERPROTEINEMIA ASSOCIATED WITH MULTIPLE MYELOMAS. W. A. PERLZWEIG, GEORGES DELRUE and CHARLES GESCHICKTER, J. A. M. A. **90**:755, 1928.

In an unusual case of hyperproteinemia associated with multiple myelomas the great increase of the plasma protein was found to be almost entirely in the euglobulin and partly fibrinogen fractions. It is possible that this phenomenon may be explained on the basis of a systemic reaction to a foreign protein.

AUTHORS' SUMMARY.

ON THE NATURE OF BLOOD CREATININE. O. H. GAEBLER and A. K. KELTCH, J. Biol. Chem. **76**:337, 1928.

Procedures are outlined for the isolation of creatinine from blood and transudate. Creatinine potassium picrate has a wide range of solubilities under various conditions. Details are given for practically complete precipitation of creatinine in the form of this derivative. Methods for the analysis of small quantities of creatinine potassium picrate and for conversion to creatinine zinc chloride are recorded. Attention is directed to a complex acid formed by picric acid and phosphotungstic acid. Creatinine is present in large amounts in the blood during experimental and nephritic retention, and is also present in the normal blood of cattle. The chromogenic substances other than creatinine also accumulate in the blood during retention. The present direct determinations are not a measure of any of the substances involved. A comparison of isolation data with results obtained by the use of kaolin in normal blood and in blood during retention shows that as absolute and relative amounts are altered the presence of either creatinine or other chromogenic substance may even escape detection. The bearing of the results on other problems in metabolism due to creatine and creatinine is discussed.

AUTHORS' SUMMARY.

p_H CONTENTS OF GASTRO-INTESTINAL TRACT IN DOGS, IN RELATION TO DIET AND RICKETS. D. M. GRAYZEL and E. G. MILLER, JR., J. Biol. Chem. **76**:423, 1928.

The reaction of the intestinal contents of dogs on a normal mixed diet is acid practically throughout the entire length of the tract, the cecum and colon showing somewhat less constancy in the results than the other levels of the tract. The p_H of the small intestine varies between 5.7 and 6.6. The reaction of the intestinal contents of dogs fed high fat, protein or carbohydrate diets is practically within the normal range for each level of the tract. On Mellanby's diet, known to produce rickets in puppies, the reaction of the intestinal contents of dogs tends to be more alkaline. The p_H of the small intestine varied from 6.4 to 7.4. The addition of cod liver oil to Mellanby's diet changes the intestinal reaction back to its normal range. Irradiation with ultraviolet light tends to bring the reaction of the intestinal contents of dogs on a rickets-producing diet back to the normal values. The irradiation with ultraviolet light of dogs on a normal diet does not cause any apparent change in the alimentary p_H. These facts are offered as further evidence that changes in the reaction of the alimentary contents are (through the effect on solubilities of various materials and hence on their absorption) an important factor in alterations of inorganic metabolism, and especially rickets.

AUTHORS' SUMMARY.

CHEMICAL COMPOSITION OF FLUID IN JOINT EFFUSION. F. A. CAJORI and R. PEMBERTON, J. Biol. Chem. **76**:471, 1928.

The high acidity and low sugar content of synovial fluid are probably the result of leukocytic glycolysis. The high viscosity is due to its mucin content. The globulin content varies considerably but is in slightly greater proportion to the albumin content than is normal for plasma. The nonprotein, urea and amino-acid nitrogen concentrations are practically identical with those of plasma.

ARTHUR LOCKE.

ELECTRODIALYSIS OF TUBERCULIN. F. B. SEIBERT and M. T. HANKE, J. Biol. Chem. **76**:535, 1928.

Electrodialysis does not appreciably impair the activity of tuberculin preparations. The tuberculin principle is practically nondiffusible through parchment or properly prepared collodion membranes.

ARTHUR LOCKE.

BLOOD CONCENTRATION IN MARINE FISHES. F. G. HALL, J. Biol. Chem. **76**:623, 1928.

Asphyxia produces marked changes in the constitution of the blood of fish. The concentrations of hemoglobin, phosphorus, iron, red corpuscles, total nitrogenous substance and total anhydrous substance are all increased, indicating a dehydration proportionate in extent to the duration of the asphyxia. The iron concentration increases most rapidly, and the total nitrogen most slowly. Only a part of the increased iron content is present as hemoglobin. The remainder is in a form simpler than hematin and is mobilized, perhaps, from the spleen, since that organ becomes greatly decreased in size during asphyxia. The oxygen-combining power of the blood does not increase proportionately to the hemoglobin concentration on account of an associated increase in fixed acidity.

ARTHUR LOCKE.

THE RELATION OF DIET TO THE QUALITY OF FAT PRODUCED IN THE ANIMAL BODY. W. E. ANDERSON and L. B. MENDEL, J. Biol. Chem. **76**:729, 1928.

The character of the body fat laid down by male albino rats resembles that of the food fat ingested when the latter is soy-bean, corn, cottonseed or peanut oil. A less saturated, i. e., softer or lower-melting, body fat is produced in response to the feeding of butter or coconut oil. The substitution of carbohydrate or protein for fat in the diet results in the production of comparatively hard body fats. Soft body fat can be replaced with harder fat by a procedure of fasting, followed by subsequent maintenance on the carbohydrate-type diet.

ARTHUR LOCKE.

THE INFLUENCE OF SODIUM FLUORIDE AND THYMOL ON THE DETERMINATION OF UREA BY THE UREASE METHOD. A. E. OSTERBERG and E. V. SCHMIDT, J. Biol. Chem. **76**:749, 1928.

Sodium fluoride and thymol in the proportion of 10:1, and in the concentration of 10 or more milligrams for each cubic centimeter of blood, as recommended by Sander, lead to erroneous values for urea, as determined by the Van Slyke and Cullen modification of the Marshall urease method. The action of the preservative is to retard the conversion of urea to ammonium carbonate by the enzyme. Urea, when added to either water or blood, cannot be recovered quantitatively by the Van Slyke and Cullen procedure in the presence of sodium fluoride. If a longer period of incubation is adopted the urea values approximate more closely their true value. This procedure, however, is not recommended.

AUTHORS' SUMMARY.

THE INFLUENCE OF THE PURINE DIURETICS ON INORGANIC PHOSPHATES OF BLOOD AND URINE. A. BOLLIGER, J. Biol. Chem. **76**:797, 1928.

The specific diuretic action of the purine derivatives: caffeine sodium benzoate, theobromine sodio-salicylate, theophylline and euphyllin, is correlated with their capacity to produce phosphate retention. The oral administration of caffeine to dogs may occasion the appearance of reducing substances in the urine, but it does not produce any change in the blood sugar level.

ARTHUR LOCKE.

STUDIES IN THE MICROCHEMISTRY OF THE CELL: I. THE CHROMATIN CONTENT OF NORMAL AND MALIGNANT CELLS, AS DEMONSTRATED BY FEULGEN'S "NEUCLEAL-REAKTION." R. J. LUDFORD, Proc. Roy. Soc. **102**:397, 1928.

According to Feulgen, when sections of suitably fixed material are submitted to a mild hydrolysis, treated with fuchsin-sulphurous acid and then thoroughly washed in sulphurous acid, the nucleoproteids of animal cells are stained an intense purple or violet. On the basis of this conception, the following conclusions were

drawn regarding the thymus-nucleic acid protein complexes (chromatin) of animal nuclei. During oögenesis in the rat and mouse there was not any increase in the chromatin content of the nucleus. When the germinal vesicle broke down to form the chromosomes, chromatin was not extruded into the cytoplasm. Neither the oxyphil-staining or the basophil-staining nucleoli of the oöcyte of the mollusk, *Limnoea stagnalis*, contained chromatin. The sperm heads of both *Limnoea* and of the mouse and rat stained intensely. At those stages of spermatogenesis when the chromosomes were stretched, the reaction was only faint, but it became progressively brighter with condensation. There were indications that the chromosomes contained other substances in addition to chromatin. Chromatin extrusion was not observed in epithelial cells of the epididymis. After secretory activity, the nuclei of gland cells often became shrunken and irregularly lobed. This was clearly seen in the medulla of the suprarenal, following exposure to cold. Such exhausted nuclei still stained brightly, so that it appeared that some substance other than chromatin was lost during functional activity. It was not possible to demonstrate any relationship between the amount of chromatin in a tumor cell nucleus and the rate of growth of the tumor. In sections through a tar tumor and the surrounding skin no difference was apparent in the amount of chromatin in the normal and in the malignant cells. During cellular degeneration in the tumors examined, the nuclei became shrunken. The chromatin ran together, and the whole nucleus stained intensely. The chromosomes of all the tumors examined stained intensely. During the prophase of mitosis, it was seen that the chromosomes were separate from the nucleolus. The nuclear extrusions, which were well marked in some tumors, consisted of nucleolar material and not chromatin. It was principally nucleolar extrusions which gave rise to keratohyalin during cornification. Some large nuclei contained apparently the same amount of chromatin as smaller ones, but the giant nuclei which occurred in some tumors and were formed either by irregularities of cell division or by the fusion of smaller nuclei contained large masses of chromatin.

AUTHOR'S SUMMARY.

ON THE CHEMICAL EVIDENCES OF THE ORGANIC CONTENT OF HUMAN ENAMEL. E. SPRAWSON and F. W. BURY, Proc. Roy. Soc. London **102**:419, 1928.

Human enamel may contain approximately 0.15 per cent of protein. (The analyses and sampling on which this conclusion is based were made with accuracy, precaution being taken to avoid contamination by nonenamel, protein-containing materials, such as dentine, salivary calculus, etc.)

ARTHUR LOCKE.

LIPASE IN TISSUES, PARTICULARLY IN TUBERCULOUS GRANULATION TISSUE. H. TAKEBAYASHI, Beitr. z. Klin. d. Tuberk. **67**:748, 1927.

The amount of lipase was estimated by its action on tributyrin, according to the technic of Rona and Michaelis. It was found that tuberculous granulation tissue contains usually more lipase than nonspecific granulation tissue; the same was true of tuberculous pus.

MAX PINNER.

HEMATINEMIA. G. HASELHORST, Zentrabl. f. Gynäk. **51**:3098, 1927.

From the study of fifty-three cases of abdominal pregnancy, it is concluded that hematin is demonstrable spectroscopically in the circulating blood in about one third of the cases of disturbed extra-uterine pregnancies and in about one half of the cases of tubal abortions of protracted course.

Microbiology and Parasitology

ANTENATAL INFECTION A FACTOR IN FETAL MORBIDITY. EMILE DUSKES and EVA F. DODGE, Am. J. Dis. Child. **35**:221, 1928.

The important influence of maternal infections on fetal viability and mortality is shown by a large number of cases collected from the literature in which practically every known specific disease is shown to be transmissible from mother to

fetus. The infection often occurs through apparently unruptured membranes. The channels may be (1) from the maternal circulation across the decidua, chorion and amnion, (2) from the maternal peritoneal cavity down the fallopian tubes, or (3) from the vagina through the cervical canal. The first is the most important before the onset of labor and rupture of the membranes.

Two cases of pneumococcic infection are reported, one being a fetal bacteremia following a maternal pneumococcic puerperal septicemia, the other being an old syphilitic fibrous peritonitis with a superimposed recent pneumococcic infection in a stillborn fetus of a syphilitic mother who, one week before delivery, had a sore throat from which pneumococci and other organisms were isolated.

The importance of prenatal care is stressed, since minor disabilities, even though insignificant, may lower the general resistance to such a degree that the status of the fetus is occasionally influenced extremely unfavorably. PEARL M. ZEEK.

CERTAIN BRONCHOMYCOSES WHICH MAY SIMULATE PULMONARY TUBERCULOSIS. ALDO CASTELLANI, Am. Rev. Tuberc. **16**:541, 1927.

The subject of bronchitis and broncho-alveolitis of fungal origin is considered in detail. These conditions are not rare, even in temperate climates, and an early diagnosis means the possibility of a cure. Secondary bronchomycoses are common, but the mere finding of the fungus in the sputum is not sufficient to establish a diagnosis of primary bronchomycosis; every possible investigation should be carried out to exclude tuberculosis. The article should be read in the original since it is not suitable for brief abstract. H. J. CORPER.

FUSO-SPIROCHETAL DISEASE OF THE LUNGS. DAVID T. SMITH, Am. Rev. Tuberc. **16**:584, 1927.

Clinical, bacteriologic, pathologic and experimental studies indicate that pulmonary gangrene, most cases of pulmonary abscess, certain types of unresolved pneumonia and bloody bronchitis, putrid bronchitis and primary bronchiectasis are not separate disease entities, but only different manifestations of infection with a specific group of anaerobic micro-organisms. Spirochetes (*T. microdentium, T. macrodentium, S. vincenti, S. bronchialis*), fusiform bacilli, vibrios and cocci have been found constantly in the gums of patients suffering with these infections, in the washed pulmonary sputum and in pulmonary tissue at necropsy. When material, scraped from the alveolar border of the teeth in cases of moderately severe pyorrhea, was introduced into the trachea of anesthetized mice, guinea-pigs and rabbits, a variety of pulmonary infections resulted, which resembled closely the acute and chronic manifestations of fusospirochetal disease in man. *Treponema microdentium, Treponema macrodentium,* and two types of fusiform bacilli have been isolated in pure culture from the washed pulmonary sputum.

H. J. CORPER.

PULMONARY SPOROTRICHOSIS. WILEY D. FORBUS, Am. Rev. Tuberc. **16**:599, 1927.

Pulmonary infections by sporotrichum are extremely rare, there being only two cases in the literature in which the evidence is satisfactory. Visceral lesions are almost unknown in this disease. The lesions found in the lung and spleen of a case are described. They appear somewhat similar to those produced by the tubercle bacillus, but are by no means identical with them. Attention is called to the septicemic nature of many apparently localized *Sporotrichum* infections and the associated lack of generalized visceral lesions in such cases. It is pointed out that, because of the rarity of visceral lesions in *Sporotrichum* infections, little attention need be paid to the probability of such infection in the differential clinical diagnosis of obscure pulmonary conditions. H. J. CORPER.

I. Calcium and Vitamine-D Deficiencies as Factors in Lowering Resistance to Tuberculosis in White Rats. Agnes H. Grant; B. Suyenaga; D. E. Stegeman and J. A. Bowen, Am. Rev. Tuberc. **16**:628 and 642, 1927.

White rats can be made so susceptible to tuberculosis, by decreasing the calcium and vitamin D of the diet sufficiently, that they develop tuberculosis in the lungs which can be diagnosed grossly and microscopically, and by guinea-pig inoculation. Rats receiving adequate diets both before and after inoculation are immune to subcutaneous inoculations of tubercle bacilli four and ten times as large.

Decreasing the vitamin D of the diet sufficiently decreases the resistance of white rats to tuberculosis, from a high immunity to a susceptibility to subcutaneous injections of a virulent strain of bovine bacilli. Gloomy winter weather, as it influences the amount and nature of sunlight, forces young rats to obtain a larger part of their supply of vitamin D from the diet. If the vitamin D content of the diet is low, rickets is intensified and the susceptibility to tuberculosis is increased.

H. J. Corper.

The Relation Between Loss of Acid-Fastness of the Tubercle Bacillus and Hydrogen-Ion Concentration. C. H. Boissevain, Am. Rev. Tuberc. **16**:758, 1927.

The time necessary for the loss of acid-fastness of tubercle bacilli in acids is inversely proportional to the hydrogen-ion concentration. The results are complicated by the buffering action of the tuberculo-protein. It is probable that the hydrogen ions act by hydrolyzing the acid-fast substance. The acid solution for hydrolyzing the bacilli contains an unidentified substance, which is soluble in acids and alkali, but not in fat-solvents. It is pointed out that the p_H of several fat-solvents may be responsible for their "defatting" action.

H. J. Corper.

The Isolation of Tubercle Bacilli from Septic Material. H. C. Sweany and Max Evanoff, Am. Rev. Tuberc. **17**:47, 1928.

In the routine cultivation of tubercle bacilli from various pathologic sources, it is recommended that all material, which contains only a few or no contaminating micro-organisms, be directly inoculated on several tubes of each of three or more different mediums, in such a manner as to dilute out the contaminating micro-organisms serially. One of the various veal-egg mediums has been found best, but should be supplemented by cooked glycerine-blood-agar and glycerine-potato. These two supplementary mediums are to be used because no single medium will consistently yield positive results to the exclusion of all others. When nonspore forming bacteria are present in large numbers Petroff's sodium hydroxide method is recommended. It should only be used, however, when good results cannot be obtained without it, because in one observation as many as 80 per cent of acid-fast forms were destroyed by it. Furthermore, "denatured" strains were obtained twice following its use. Gentian violet should only be used when so many spores are present that serial dilution following sodium-hydroxide treatment will not dilute them out.

H. J. Corper.

The Granules of the Tubercle Bacillus. H. C. Sweany, Am. Rev. Tuberc. **17**:53, 1928.

The granules of the tubercle bacillus in tuberculous lesions in man and guinea-pigs were studied. No rule was observed regarding the cause of granule-formation because the granules exist in apparently favorable environments, and do not exist sometimes in an unfavorable environment. Granules in certain stages of their life cycle can be made to sprout and reproduce acid-fast micro-organisms. In other stages they can be caused to sprout into actively motile bacilli that resemble certain young forms seen in bouillon cultures. These are nonacid-fast and motile.

Other granules have been observed to degenerate into coccoid forms. Others apparently go through a gonidiform stage, in which granules are held together in a matrix, and may sprout again in a way similar to the free granules. These granules are capable of producing tuberculosis in guinea-pigs when picked out by the single cell method. They are also capable of producing pure cultures of tubercle bacilli. A semi-acid-fast moldlike growth was also obtained having tuberculogenic properties, and ultimately regaining complete acid-fast properties on animal passage. Very small doses of granules produce atypical and chronic tuberculosis, while a typical form results from larger doses. H. J. CORPER.

THE FILTRABILITY OF THE TUBERCLE BACILLUS. H. C. SWEANY, Am. Rev. Tuberc. **17**:77, 1928.

A virus exists in tuberculous lesions that is capable of passing through the finest Berkefeld filters and producing varying grades of disease in guinea-pigs, depending on the particular virus. The atypical types of tuberculosis produced proves that some of the filtrable forms are not tubercle bacilli, yet they possess sufficient intrinsic quality to regenerate tubercle bacilli on passage. This suggests also a relationship to the lymphogranuloma. H. J. CORPER.

RECURRING STRAINS OF HERPES VIRUS. SIMON FLEXNER, J. Exper. Med. **47**:9, 1928.

In this paper, three strains of the herpes virus have been dealt with. The H. F. II strain was obtained from the subject H. F. four years after the H. F. I strain was secured. H. F. had recurrent herpes. If the subject is also a chronic carrier of the herpes virus, then it is not one, but two or more strains which are persistently carried. The H. F. II strain is of mitigated pathogenic action for the rabbit, as compared with the H. F. I strain; it is to be classed as dermatotropic rather than neurotropic. And yet, in the subject there was no indication that the attack of herpes provoked was different from the other attacks associated with the H. F. I virus. The other two herpes strains derive their interest from the fact that they came also from persons who suffer from repeated attacks of labial herpes. One strain proved highly neurotropic, resembling in this respect the H. F. I strain; the other was hardly neurotropic at all, but was none the less definitely dermatotropic. It may be possible at a later date to secure other samples of virus from these individuals for comparison. The dermatotropic F. strain penetrates to the central nervous system far more readily and certainly from the skin than from corneal surfaces. The recovered inoculated rabbits showed only relative protection to reinoculation of the herpes virus. A notable difference appeared in the degree of protection acquired, on the one hand by the cornea and on the other by the brain. While the one was partial, the other was complete. The complete resistance of the brain was shown (*a*) by the complete failure of the intracerebral inoculation, and (*b*) by the absence of circling movements following corneal inoculation. AUTHOR'S SUMMARY.

HERPES VIRUS ENCEPHALITIS IN THE GUINEA-PIG. SIMON FLEXNER, J. Exper. Med. **47**:23, 1928.

The guinea-pig is subject to cerebral and corneal inoculation of the herpes virus. The effects of the inoculations vary with the strength or degree of virulence of the virus. Weak strains of the virus are implanted on the cerebrum with difficulty and strong strains with ease. Weak strains are quickly suppressed by the brain and strong strains may be passed indefinitely from brain to brain of the guinea-pig. Strains of intermediate potency can be passed for a limited number of times only. Weak strains induce keratoconjunctivitis without involvement of the brain, while strong strains invade the brain from the eye and produce fatal encephalitis. In the latter case, the brain contains active virus inoculable on the

cornea and into the brain of rabbits and guinea-pigs. Strains of intermediate potency produce keratoconjunctivitis accompanied by mild symptoms of encephaltis, from which recovery results. The guinea-pig serves even more definitely than the rabbit to distinguish grades of virus according to strength or virulence. There is no difference of kind but only of degree of response to inoculation of herpes virus in the rabbit and the guinea-pig. The etiology of epidemic encephaltis has not, therefore, been brought appreciably nearer solution by experiments with herpes virus carried out in guinea-pigs.

AUTHOR'S SUMMARY.

ULTRA-VIOLET LIGHT AND VACCINE VIRUS. THOMAS M. RIVERS, HENRY STEVENS and FREDERICK L. GATES, J. Exper. Med. **47**:37 and 45, 1928.

Rabbit skin subjected for a few minutes to ultraviolet light and then inoculated at once with vaccine virus is less susceptible to the action of the virus than is untreated skin. If twenty-four, forty-eight or seventy-two hours elapse between the time of irradiation and inoculation, the treated skin appears to be more susceptible than is untreated skin. Skin repeatedly exposed to ultraviolet light is less susceptible to the action of vaccine virus than is nonirradiated skin. Under the experimental conditions described in the present paper, it was found that the amount of energy required to kill staphylococci at single wave-lengths in the active ultraviolet region was approximately the same as that necessary to inactivate vaccine virus.

AUTHORS' SUMMARY.

METHODS OF ISOLATING A BACTERIOPHAGE FOR BACILLUS DIPHTHERIAE. JULIUS A. KLOSTERMAN and KATHRYN W. SMALL, J. Exper. Med. **47**:121, 1928.

Of the attempts to isolate an antidiphtheria phage (1) from stools collected daily during the course of a case of the disease, (2) from a 33 day old broth culture of *B. diptheriae,* (3) from intestinal contents and peritoneal washings of guinea-pigs inoculated with three different toxic strains of *B. diphtheriae,* none yielded an antidiphtheria phage. However, of eleven specimens of feces collected from eleven antitoxin horses one was found to contain a bacteriophage active against *B. diphtheriae.* This phage was not observed in the first generation and did not show up until transferred the second time. Had the results of the first transfer been regarded as final in all certainty the existence of a phage would not have been recognized. Two additional specimens of feces from the positive horse were later tested to determine whether this bacteriophage was continually present in the intestinal tract of this animal. Both of these feces filtrates failed to yield a phage. Later, a sample of freshly collected blood serum from the same horse was tested and found not to contain a phage. The antidiphtheria phage was tested against eighteen nondiphtheria strains of micro-organisms to determine whether it would show lytic activity for related or unrelated bacteria. There was no evidence of lysis in any of these types. The specificity of this phase was also tested on nine strains of *B. diphtheriae* and found to be active on three heterologous strains (strain M 1314, strain F and strain G). These incidentally were all recently isolated. It failed to lyse the remaining six strains of which five were recently isolated. *B. diphtheriae* strain M 1314 was used in combination with nine heterologous bacteriophages isolated from various sources, to determine if any of these phages would by chance lyse this culture. The results were all negative. To date this phage fails to show complete lysis although the twenty-second generation has a titer of 1×10^{-9}.

AUTHORS' SUMMARY.

STREPTOCOCCUS BACTERIOPHAGE. GREGORY SHWARTZMAN, J. Exper. Med. **47**:151, 1928.

A series of experiments was carried out on various strains of streptococci in order to ascertain the changes which bacteriophage produces in the phenomena

of agglutination of these organisms. The results can be placed in the following categories. Loss of specific agglutinability was observed with partial and with what appeared as complete loss of specific agglutinin absorption and agglutinogenic properties. Partial modification of the antigen, bringing about inagglutinability of the strains with complete preservation of agglutinogenic and agglutinin-absorption properties. Coincidentally, additional components appeared. Some of these were related to the specific antigens of the organisms from which they were derived, while others were not. In two instances, these components were of "group" character. "Complete" modification observed with two strains consisting of complete transformation of the normal culture agglutinogens into antigens of an entirely different specificity. It appears from these studies that the bacteriophage phenomenon may play an intricate rôle in serologic grouping of various strains of pathogenic streptococci.

AUTHOR'S SUMMARY.

ETIOLOGY OF OROYA FEVER. BACTERIUM PERUVIANUM, N.SP., A SECONDARY INVADER OF THE LESIONS OF VERRUGA PERUANA. HIDEYO NOGUCHI, J. Exper. Med. **47**:165, 1928.

A minute, pleomorphic, motile, gram-negative bacterium has been isolated from two specimens of nodular tissue from human verruga. In films and sections of the original tissues the organism in question is difficult to distinguish from *Bartonella bacilliformis*, with which it was associated, and even in pure culture it has a number of properties in common with that parasite. Sugars are not fermented by it, it is an obligate aerobe, the optimum temperature for its growth is 25 C., and it has from two to four spiral flagella attached to one end of the body. It is, however, readily cultivated on any ordinary culture medium. Broth cultures contain much mucin, but no hydrogen sulphide is formed. Coagulated serum is liquefied by its growth and the red corpuscles in a blood agar plate are hemolyzed. Rabbits, guinea-pigs, rats and mice develop acute, fatal septicemia as a result of intravenous or intratesticular inoculation of young cultures. The liver is characteristically affected and shows a general parenchymatous degeneration and necrosis; the entire gastro-intestinal tract is intensely congested, and numerous hemorrhagic areas are present; the spleen, dark and soft, is rarely much enlarged; the kidneys are swollen and congested; the suprarenals are much swollen and intensely red; the lungs are sometimes congested but otherwise normal. In the case of intratesticular inoculation the scrotum and testicle both undergo rapid gangrene. In monkeys, septicemia has not been observed, but a violent local reaction — swelling, congestion, sometimes necrosis — follows intradermal inoculation. Since no micro-organism corresponding in character with this one has previously been described, it is regarded as a new species, and because of its presence in material obtained from Peru it has been given the name *Bacterium peruvianum*. The significance of the association of *B. peruvianum* with *Bartonella bacilliformis* deserves further investigation; it is not impossible that the two organisms are introduced into the human body by the same blood-sucking insect.

AUTHOR'S SUMMARY.

STUDIES IN THE COMMON COLD. KATHERINE C. MILLS, G. S. SHIBLEY and A. R. DOCHEZ, J. Exper. Med. **47**:193, 1928.

A study of the gram-negative, filter-passing, anaerobic organisms, described by Olitsky and Gates, and Gates and McCartney, has been undertaken with a view to determining their general character and their possible rôle in the causation of the common cold. These organisms seem to constitute part of the normal flora of the upper respiratory tract and would seem to bear no etiologic relationship to the common cold.

AUTHORS' SUMMARY.

PARATYPHOID INFECTION IN GUINEA-PIGS. JOHN B. NELSON, J. Exper. Med. **47**:207, 1928.

The course is considered of a second type of Salmonella infection naturally appearing in a guinea-pig population during the endemic stage of an earlier outbreak. After a quiescent period of five months, the percentage mortality increased abruptly; it fluctuated, with a second rise during the ninth month, and then declined. With the exception of a high rate during the second month, the percentage mortality from the initial infection tended to remain on a low level. The spread of infection in the cages of the breeding stock is recorded from the time of the first fatal case. There was a slow but general dissemination of the second organism through the group. Fatal cases were confined solely to the sows. It is suggested that a lowered individual resistance occurring during pregnancy might be associated with the irregular cage spread and with the apparent difference in susceptibility of the sexes. Natural host resistance, virulence of the organism and acquired host resistance are discussed from the standpoint of their bearing on the unequal distribution of deaths from the two infections.

AUTHOR'S SUMMARY.

A COMPARISON OF THE SPIROCHETE OF YELLOW FEVER WITH THE LEPTOSPIRA OF WEIL'S DISEASE. ERICH MARTINI, J. Exper. Med. **47**:255, 1928.

The most noteworthy point observed is the extraordinary duration of life and the relatively meager requirements for sustenance of *Leptospira icteroides*. It is conceivable that under natural conditions opportunities might arise for the prolonged existence of *Leptospira icteroides*, so that possibly after a lapse of years, the disease might reappear without introduction from outside. At any rate, the great viability of *Leptospira icteroides* must be considered in this connection. A decrease in the virulence of the leptospira does not rule out the possibility of a renewed outburst of yellow fever, since Uhlenhuth and Zuelzer have shown that it is possible to set up Weil's disease in guinea-pigs by means of apparently saprophytic spirochetes obtained from drinking water, when the virulence of these organisms has been artificially heightened.

AUTHOR'S SUMMARY.

ANATOMIC DIAGNOSIS OF YELLOW FEVER. W. H. HOFFMANN, J. Trop. Med. **31**:1, 1928.

Owing to the simplicity of the histologic diagnosis, and because it is superior to any other method, Hoffmann urges that it should be made obligatory in every fatal case the cause of which is unknown, whenever there is a possibility of yellow fever, and especially in the endemic territory of West Africa, as it is actually the only objective and reliable diagnostic basis for a systematic campaign. An international regulation of the whole problem is indispensable, because a satisfactory result under the prevailing difficulties can be obtained only by the unrestricted cooperation of all the countries interested.

TULAREMIA AMONG MEADOW MICE IN CALIFORNIA. J. C. PERRY, Pub. Health Rep. **43**:260, 1928.

Two meadow mice (*Microtus californicus-estuarinus*) collected in nature in Contra Costa County, Calif., where large numbers of sick and dead mice were found, were sent to the United States Public Health Service plague laboratory in San Francisco for examination on Sept. 24, 1927. Spleens of the wild mice were inoculated into white mice, white rats, and guinea-pigs, causing the typical lesions of tularemia, and from the latter *Bacterium tularense* was isolated. The organism was a slender, short rod, gram-negative, nonmotile, and grew only on coagulated egg yolk and blood dextrose cystine agar, and not on ordinary plain agar. It was agglutinated out to the full anti-*tularense* titer (1:1,280) of a known anti-*tularense* serum. Sections of the liver of infected white mice showed the hepatic cells

packed with these organisms. Spleen tissue rubbed on the abraded skin of a guinea-pig caused its death with the typical lesions of tularemia—caseous lymph glands, spotted spleen and spotted liver.

This is the first record of *Bacterium tularense* having been isolated from naturally infected wild mice.

AUTHOR'S SUMMARY.

MALTA FEVER: A PROBLEM FOR STATE AND MUNICIPAL LABORATORIES. A. V. HARDY, Pub. Health Rep. **43**:503, 1928.

An examination for Malta fever should be done routinely on all blood specimens sent to state or municipal laboratories for Widal tests. A rapid and preliminary test may be made to eliminate the negatives, but a careful study should be made on all doubtful and positive specimens. Dried blood specimens as well as serums should be examined. The procedure for this test is described. A diagnosis should be established only if clinical and laboratory observations agree. Malta fever in Iowa presents a health hazard comparable to that of typhoid. State and municipal laboratories have an unusual opportunity in contributing to the study of Malta fever.

AUTHOR'S SUMMARY.

THE SIZE OF HERPES VIRUS PARTICLES. S. P. BEDSON, Brit. J. Exper. Path. **8**:470, 1927.

Ultrafiltration of the herpes virus is studied in detail to determine why it is held back by the most porous Chamberland and Berkefeld filters. When a mixture of animal tissue and virus is filtered through certain membranes, titration of the virus and the protein before and after filtration reveals no attachment between virus and protein particles since the latter pass freely into the filtrate while the former remains in the residue. By repeatedly washing and refiltering this residue, each time titrating its potency by animal inoculation, none of the virus is found to be lost through adsorption by the membrane. The only membranes which allow the passage of the virus are those which also permit bacteria to pass through. Therefore, it is concluded that the herpes virus is held back only because of its size. Work is now in progress to determine whether or not it is within the limits of visibility.

PEARL M. ZEEK.

THE MONOCYTES OF THE RABBIT IN B. MONOCYTOGENES INFECTION: A STUDY OF THEIR STAINING REACTIONS AND HISTOGENESIS. L. J. WITTS and R. A. WEBB, J. Path. & Bact. **30**:687, 1927.

The authors studied the monocytes of the rabbit by producing a monocytosis through the injection intravenously of sublethal doses of *B. monocytogenes*. It is possible in this way to increase the monocytes in the blood from the normal 5.5 per cent to 30 or even 50 per cent while the polymorphonuclears and the lymphocytes remain comparatively unchanged. The monocytes were stained supravitally with neutral red and Janus green in order to differentiate them from lymphocytes and clasmatocytes. Lymphocytes take up little or no neutral red and their mitochondria which stain well with Janus green are concentrated around the nucleus. In the monocytes the mitochondria are scattered throughout the cytoplasm, but the distinctive feature of these cells is the way they segregate neutral red in a roset of particles and vacuoles around the centrosphere. Clasmatocytes ingest larger granules and vacuoles of neutral red which lie irregularly in the cytoplasm and obscure the centrosphere, while their mitochondria are rarely seen.

The monocytes of the rabbit differ from the monocytes of man in that they do not contain dustlike neutrophil granules and do not give the oxydase reaction. All the monocytes in man and the rabbit take up neutral red in a roset pattern when supravitally stained.

The monocytosis of *B. monocytogenes* infection is characterized by a regular rise and fall which is in every respect like the rise and fall of the polymorphonuclears in the leukocytosis of other infections. The monocytes are evenly distributed in the circulation and do not appear in showers.

The monocytes of the rabbit arise in the spleen and the bone marrow and are not formed in the lymph glands or liver.

Illustrations consist of two plates in colors.

E. M. HALL.

THE "CHEMOTHERAPY" OF EHRLICH AND CERTAIN GENERAL PRINCIPLES WHICH SHOULD BE APPLIED IN THE TREATMENT OF ALL INFECTIOUS DISEASES. ALMROTH E. WRIGHT, Ann. de l'Inst. Pasteur **41**:1243, 1927.

This paper is general in nature, discussing the terminology of Ehrlich and his views of chemotherapy (or "pharmacotherapy," as preferred by the author), and proceeding thence to a discussion of the mechanism and principles of the action of chemical agents in pathologic conditions.

M. S. MARSHALL.

STREPTOCOCCI AND ANTISTREPTOCOCCUS IMMUNIZATION. L. COTONI, E. CÉSARI and others, Ann. de l'Inst. Pasteur **41**:1270, 1927.

The authors present a study, whch extended over a considerable period of time, of 136 strains of streptococci, of which 97 were from various human sources, and 36 were from births or animals. Cultural characteristics, biochemical properties, pathogenicity, and attempts to immunize are reported, and it is emphasized that immunization in mice, in rabbits, and in horses is a difficult procedure with irregular results.

M. S. MARSHALL.

VARIATIONS IN THE VIRUS OF HERPES AND IN THE VIRUS OF ENCEPHALITIS LETHARGICA. C. LEVADITI, V. SANCHIS-BAYARRI and L. REINIE, Ann. de l'Inst. Pasteur **41**:1292, 1927.

The virus of herpes and the virus of epidemic encephalitis admit of varieties of unequal virulence. Their pathogenic activity may become attenuated in spite of regular passages in the brains of rabbits. The most virulent strains multiply distinctly more rapidly than do attenuated strains. The unequal receptivity of animals explains the variability of results of inoculation in series, along with the spontaneous arrest of passages, observed with weakly pathogenic herpes virus.

AUTHORS' SUMMARY.

INCUBATION IN RABIES. B. PERDOMO HURTADO, Revista de Med. y Chir. **10**:160, 1927.

In a child, aged 10, bitten by a rabid dog, the incubation period extended to 103 days. The patient died after seven days of illness. The long incubation may have been due to the action of the treatment, which was started two days after the bite, or to the injury being in the leg.

PNEUMONOMYCOSIS PENICILLINA, AN INDUSTRIAL DISEASE. R. NUSSBAUM and T. BENEDEK, Beitr. z. Klin. d. Tuberk. **67**:756, 1927.

This is a clinical and bacteriologic report on a patient who had worked for a long time with woods and who developed an acute and rapidly terminating disease. His chief complaints were dyspnea, continuous cough and weakness. In the abundant and frequently hemorrhagic sputum, tubercle bacilli could not be demonstrated. A fungus, *Penicillium bicolor*, was isolated from the sputum. This fungus is pathogenic for white rats and for rabbits. The organism could be isolated again from the lesions in the infected animals. The roentgen-ray picture of the patient simulates a fast growing tumor. An autopsy could not be performed.

MAX PINNER.

STUDIES ON PSEUDOTUBERCLE BACILLI (PSEUDOTUBERCULOSIS RODENTIUM) FROM HUMAN PATHOLOGIC FOCI. A. HAIM and KEMAL, Betitr. z. Klin. d. Tuberk. **68**:128, 1928.

The organisms in question were isolated by E. Fraenkel, one from a child, 10 weeks old, and two from twins, one 2 days and the others 4 days old. In these studies, the mode of growth on different mediums, their virulence and their immunizing properties in rabbits, guinea-pigs and white mice are reported.

MAX PINNER.

SEPSIS CAUSED BY MICROCOCCUS CATARRHALIS. H. NAGELL, München. med. Wchnschr. **75**:124, 1928.

A man, aged 19, had a septicemia caused by *M. catarrhalis* which was isolated from the blood four times, and identified in skin lesions. The illness continued three months and was followed by recovery.

E. F. HIRSCH.

THE INCUBATION PERIOD OF TYPHOID. M. KNORR, München. med. Wchnschr. **75**:255, 1928.

The incubation period of typhoid is dependent chiefly on the method of infection. In food poisoning when many organisms are evenly distributed, incubation periods of three days were observed, but individual disposition and the number of ingested organisms may be so variable that the incubation period may extend to twenty-nine days. With contact and laboratory infections the interval was from thirty-one to twenty-one days, the middle periods ranging between nine and fifteen days. The uneven distribution of the organisms in a water epidemic introduces marked variations.

AUTHOR'S SUMMARY.

BACTERIUM ABORTUM INFECTION IN MAN. M. KRISTENSEN, Ugesk. f. Laeger **89**:1123, 1927. K. GAARDE, ibid., p. 1141.

Kristensen discusses a group of eighty-nine cases giving agglutination suggesting infection with *Bacterium abortum*. He holds that this infection should be included with infection due to *B. melitensis* as undulant fever. Gaarde describes a case of septicemia in a boy, aged 16 years, accompanied by hemorrhages from the nasal and pharyngeal membranes as well as from the kidney, and by a purpura-like eruption. Agglutination tests gave results that indicated infection with *Bacterium abortum*.

Immunology

CUTANEOUS REACTION IN THE NORMAL RABBIT TO MATERIAL FROM SMALLPOX LESIONS. NEIL E. MCKINNON and ROBERT D. DEFRIES, Am. J. Hyg. **8**: 93, 1928.

Intradermal injections into normal rabbits of a saline emulsion of material from known cases of smallpox were regularly followed within three days by red indurated elevations. Although constantly present, these lesions varied considerably in size and minor characteristics. When subsequently treated with vaccine virus, these rabbits responded differently from animals not previously inoculated. Material from cases of chickenpox failed to elicit reactions characteristic of material from cases of smallpox. The injection of material from cases of smallpox into the skin of vaccine-immunized rabbits evoked a reaction of an allergic nature which differs sharply from the reaction of the normal rabbits, and this is advocated as a reliable diagnostic procedure.

S. D. SIMON.

THE LABORATORY DIAGNOSIS OF SMALLPOX VIRUS UTILIZING THE RABBIT. ROBERT D. DEFRIES and NEIL E. MCKINNON, Am. J. Hyg. **8**:107, 1928.

Two laboratory tests for the diagnosis of smallpox have been used in the past, namely, the allergic reaction observed in rabbits previously immunized with vaccine

virus, and the corneal reaction (of Paul). The first of these was found to vary immoderately both in occurrence and in character, and the second, while specific, was positive in only about one half of the tests when material from known cases of smallpox was used. The test of choice is found in the regular reaction following intradermal inoculation in the normal rabbits as contrasted with the response following similar treatment in the vaccine-immunized rabbit.

S. D. SIMON.

HETEROPHILE ANTIGEN AND ANTIBODY. A STUDY OF ANTICHICKEN HEMOLYTIC SERUMS. R. ROSCOE HYDE, Am. J. Hyg. **8**:205, 1928.

From a large number of experiments, the following conclusions were reached: The red corpuscles of the chicken contains heterophil antigen, since it incites in the rabbit a true heterophil antibody. The complementing properties of serums cannot be used as an index of their species relationships, nor can hemolytic antibodies be used as an index of the species relationships of the source of their antigens. Absorption tests on antichicken rabbit hemolysin with the native cells of the chicken and sheep demonstrate that at least two amboceptors are present. Antichicken rabbit hemolysin differs from homologous antisheep rabbit hemolysin in that the latter does not sensitize chicken corpuscles to the guinea-pig complement. Immune serums of heterophil type are nontoxic for the complement-deficient guinea-pig, and they do not cause positive skin reactions; this failure to react is not to be explained on the basis of simple lack of complement. The red cells of the chicken and sheep seem to stand in the following relation to each other as determined by their immune rabbit amboceptors, when activated with guinea-pig complement:

1. Chicken cells: (*a*) Chicken cells do incite hemolysins for sheep cells. (*b*) Boiled chicken cells do absorb hemolysins incited by sheep cells as shown by their titer for sheep cells. (*c*) Chicken cells do not become sensitized to hemolysins incited by sheep cells.

2. Sheep cells: (*a*) Sheep cells do not incite hemolysins for chicken cells. (*b*) Boiled sheep cells do not absorb hemolysins incited by chicken cells as shown by their titer for chicken cells. (*c*) Sheep cells do become sensitized to hemolysins incited by sheep cells.

S. D. SIMON.

LOCAL SPECIFIC THERAPY OF EXPERIMENTAL PNEUMOCOCCAL MENINGITIS. FRED W. STEWART, J. Exper. Med. **47**:1, 1928.

In experimental type 1 pneumococcal meningitis of dogs, involvement of the central cord is common after the second day of the disease. These lesions of the central cord may progress toward extensive suppurative myelitis. Abscesses are infrequent; they arise either as direct perivascular extensions of the meningeal disease or at the site of infected purpuric lesions. In prolonged cases of untreated meningitis in reinfected animals, nothing resembling the disappearance of exudate following crisis in pneumonia occurs. The tendency is toward organization. Late lesions are characterized by the marked development of a perivascular clasmatocytic apparatus, similar to, but more extensive than, that hitherto reported in experimental herpetic encephalitis.

AUTHOR'S SUMMARY.

THE PRECIPITIN REACTION OF ANTIPNEUMOCOCCUS SERUMS. HARRY SOBOTKA, MAE FRIEDLANDER and EDWIN J. BANZHAF, J. Exper. Med. **47**:57, 79, 1928.

The mechanism of the precipitin reaction between antipneumococcus serums and the type-specific soluble carbohydrate was investigated. The sensitivity of the reaction was found to be generally constant when expressed by the product of the concentrations of the two reacting substances. Precipitin index (p. I.) is defined as one millionth of the reciprocal value of this product. Zonal phenomena and their bearing on the absolute concentration and the equivalent weight of the antibody are discussed. The greater tendency toward exhibition of a postzone in type III is

connected with the lower acid equivalent of the homologous specific carbohydrate. The influence of the addition of normal serum and the influence of slight changes in the p_H are studied. The addition of normal serum as well as the increase in the p_H promote the prozone, whereas decrease in the p_H promotes the postzone. The sensitivity of the reaction is accordingly influenced by the p_H in different ways, depending on the range of concentration. The precipitin index allows the recognition and elimination of zonal irregularities. Thus it offers a method for the standardization of pneumonia antibody. The precipitin indexes for a number of monovalent and polyvalent antipneumococcus serums were determined under known conditions, and found to vary as did the number of protective units. The ratio precipitin index protective units in monovalent serums was found to lie between 2.8 and 4.8 for type I and to be about ten times greater for type III. Lower values were found in polyvalent horse serums and in heterologous monovalent serums when mixed with each other. The influence of the duration of treatment on the quotient was studied. Several refined and concentrated preparations showed a relative increase in precipitin activity.

AUTHORS' SUMMARY.

THE ANTIGENIC COMPLEX OF STREPTOCOCCUS HEMOLYTICUS. REBECCA C. LANCEFIELD, J. Exper. Med. **47**:91, 1928.

Hydrochloric acid extracts of *Streptococcus hemolyticus* contain type-specific, as well as nontype-specific, substances. The precipitates formed by these crude extracts with homologous antibacterial serum are flocculent, while those obtained with heterologous serum are usually disklike. The type-specific substances may be detected by the use of antibacterial serums absorbed with heterologous strains of hemolytic streptococci. Such absorbed serums are type-specific; they are precipitated only by extracts of strains of the homologous type. Any heterologous strain of hemolytic streptococcus absorbs the antibodies for all other heterologous strains, but homologous strains absorb type-specific antibodies as well. Numerous repeated absorptions with heterologous hemolytic streptococci tend to lower the titer of the type-specific antibody. A possible explanation of this fact is suggested. Three strains did not yield a type-specific substance; and it seems probable that they had lost this function because of long continued cultivation in artificial mediums. Classification based on the precipitin test with absorbed serum agrees with that previously determined by agglutination and protection tests. The method is, therefore, applicable to the problem of classification of the hemolytic streptococci.

AUTHOR'S SUMMARY.

THE INFLUENCE OF HEATING THE IMMUNIZATION MATERIAL ON THE ANTIBODY-INVOKING EFFECTIVENESS OF THE TYPE-SPECIFIC AND SPECIES-SPECIFIC ANTIGENS OF TYPE II PNEUMOCOCCUS CELLS. EMIDIO L. GASPARI, JOHN Y. SUGG, WILLIAM L. FLEMING and JAMES M. NEILL, J. Exper. Med. **47**: 131, 1928.

This paper presents an experimental comparison of the effect of heating of the immunization material on the antibody-invoking effectiveness of the type-specific (SP) and species-specific (P) antigens of type II pneumococci. Heating of the pneumococcus suspension (vaccine) invariably decreased the production of species-specific antibodies (anti-P) without a comparable effect on the production of type-specific antibodies (anti-S). For diagnostic typing purposes, the ideal anti-pneumococcus serum should contain the maximum content of type-specific, and the minimum of species-specific antibody. Our results with forty-one rabbits indicate that the ideal serum from the type-specific standpoint would be obtained by immunization with the heated cells of virulent pneumococci over a comparatively short period of immunization; and that the only thing gained by continued immunization or by the use of unheated bacteria at any stage of the immunization is an increase in the species-specific antibody which is undesirable in serums to be used for diagnostic purposes.

AUTHORS' SUMMARY.

ON PRECIPITABLE SUBSTANCES DERIVED FROM BACILLUS TYPHOSUS AND BACILLUS PARATYPHOSUS B. J. FURTH and K. LANDSTEINER, J. Exper. Med. **47**:171, 1928.

Attempts to confirm certain statements that ether-soluble specific substances can be obtained from *Bacillus typhosus* have led to negative results. Two serologically active protein substances and another that was nonprotein have been separated from *B. typhosus*. The first two are not resistant to tryptic digestion or to treatment with alkaline hypochlorite solution, whereas the third resists both. One of the proteins could be extracted with 75 per cent alcohol. Specific precipitable substances reacting like the nonprotein substance of *B. typhosus* and containing large amounts of carbohydrates have been prepared from *B. paratyphosus* B, *B. enteritidis*, and *Proteus HX19* and *0X19*. Observations on the serologic behavior of these preparations are described.

AUTHORS' SUMMARY.

THE EFFECT ON SUBSEQUENT AGGLUTINATION OF THE EXPOSURE OF BACTERIA TO HEATED ANTISERUM. F. S. JONES, J. Exper. Med. **47**:245, 1928.

It is shown that when dilute rabbit serum rich in agglutinin for the hog-cholera bacillus is heated at 75 C. for twenty minutes and the bacilli incubated with the heated serum, agglutination fails to result on the addition of unheated immune serum. When the immune serum is first heated to 80 C., it no longer greatly inhibits secondary agglutination when the organisms are exposed to fresh agglutinin. The abortion bacillus agglutinin acts in a similar manner, except that the immune serum must be heated above 80 C. for twenty minutes to prevent the second agglutination. The reactions are specific, since control experiments with normal rabbit serum heated at various temperatures failed to influence further agglutination. It has also been shown by precipitation tests that there is definite fixation of serum proteins and bacterial cells with the heated serums which would prevent subsequent agglutination. Furthermore, heated antiserum which would prevent the secondary agglutination still possessed the property of deviating complement in a hemolytic series.

AUTHOR'S SUMMARY.

THE RÔLE OF THE RETICULO-ENDOTHELIAL SYSTEM IN IMMUNITY. C. W. JUNGEBLUT, J. Exper. Med. **47**:261, 1928.

Blockade of the reticulo-endothelial system by means of one intravenous injection of India ink as well as splenectomy did not alter the course of either pneumococcus type I infection or tetanus intoxication in mice. The protective action of antipneumococcus type I serum against the corresponding infection, as determined by the injection of in vitro prepared mixtures of serum and culture, was definitely lower in mice that had received one blocking injection of India ink shortly before the test. Titration of tetanus toxin and antitoxin in blocked and splenectomized mice gave results identical with those obtained in normal mice, if in vitro prepared and incubated toxin-antitoxin mixtures were injected. The degree of protection, however, conferred by a preceding dose of antitoxin against subsequent intoxication, was markedly lower in blocked mice than in normal control animals, this difference becoming more pronounced with the increase of the time interval.

AUTHOR'S SUMMARY.

A STUDY OF THE MECHANISM OF RECOVERY FROM EXPERIMENTAL PNEUMOCOCCUS INFECTION. OSWALD H. ROBERTSON, SHUTAI T. WOO, SHEO NAN CHEER, and LI PIN KING, J. Exper. Med. **47**:317, 1928.

A study was made of the blood of cats and rabbits during experimental pneumococcus infection with a view to ascertaining the relationship of acquired immune properties to the mechanism of recovery. Observations were directed chiefly toward the detection of pneumococcidal promoting substances, but the other manifestations of antipneumococcus reaction were studied as well. It was found con-

stantly that the serum of animals recovering from infection possessed the power to promote the destruction of highly virulent pneumococci in rabbit serum-leukocyte mixtures which mixtures of themselves have no growth inhibitory action. Furthermore, the presence of this serum immunity was associated with a marked increase in acquired resistance to the pneumococcus. In cats that were studied in the most detail, the pneumococcidal promoting power of the serum as well as the opsonic, agglutinative and mouse protective activities became demonstrable at the time of recovery, and their appearance in the serum always marked the termination of invasion of the blood. These immune reactions were found to be type-specific. The animals that succumbed failed to develop detectable serum immune properties and showed persistent invasion of the blood. The degree of leukocytosis did not appear to bear any constant relation to the outcome of the disease. The significance of these observations is discussed.

AUTHORS' SUMMARY.

ON THE RÔLE OF CARBOHYDRATE HAPTENS IN BACTERIAL ANAPHYLAXIS. JOSEPH TOMCSIK and T. J. KUROTCHKIN, J. Exper. Med. **47**:379, 1928.

In passively sensitized animals bacterial anaphylaxis has been produced, in vivo and in vitro, with haptens from *Bacillus lactis-aërogenes*, the pneumobacillus and a yeast. The smallest amount of hapten causing fatal anaphylaxis is less than the minimal amount of protein which will cause death in properly sensitized animals. The haptens used were largely carbohydrates, and gave none of the protein reactions, but since they contained a small amount of nitrogen, it cannot be asserted definitely that carbohydrate alone will produce shock. Since haptens will not sensitize animals, it must be concluded that the anaphylactogenic and shock-producing parts of the antigen are not identical. These experiments provide further evidence of the close relationship of precipitins to anaphylaxis.

AUTHORS' SUMMARY.

ALLERGIC IRRITABILITY IN GUINEA-PIGS. PAUL A. LEWIS and DOROTHY LOOMIS, J. Exper. Med. **47**:437, 1928.

The allergic irritability of closely inbred guinea-pigs as represented by their capacity to produce hemolytic antibodies for beef and sheep corpuscles, and agglutinins for *Bacillus typhosus* and *Bacillus abortus* (Bang) differs by families, and therefore is at least partly dependent on inherited characteristics. These differences show an imperfect but suggestive correlation with the differences in the resistance of the same families to inoculation tuberculosis as previously determined by Wright and Lewis. The differences in production of the antibodies also show an imperfect correlation with the differences in response in the anaphylactic reaction complex as previously determined by Lewis and Loomis. These studies suggest strongly that the allergic irritability is one of the several inheritable characters which form a partial basis for the natural resistance to tuberculosis. The antibody-producing capacity is satisfactorily defined only when minimal or moderate amounts of antigen are used and this in single treatments. The irregularities in experimental results when repeated treatments or large single treatments are used suggest that the production of antibodies in the second or "acquired capacity" phase may rest on a somewhat different fundamental basis than the latent or potential natural capacity. There is some slight evidence that production in the second phase may also be influenced by inherited qualities.

AUTHORS' SUMMARY.

THE ANTIGENIC COMPLEX OF STREPTOCOCCUS HEMOLYTICUS. REBECCA C. LANCEFIELD, J. Exper. Med. **47**:469, 1928.

The chemical and immunologic characteristics of the type-specific substance (M) of *Streptococcus hemolyticus* are considered. A summary of the evidence for the protein nature of this substance follows: It is precipitated by the usual protein precipitants such as dilute alcohol, dilute acetic acid and picric acid. It contains

14 per cent protein nitrogen after considerable purification. It is progressively destroyed by removal of the NH_2 group by treatment with nitrous acid. It is completely and readily digested by trypsin and by pepsin. "Purified" extracts react in relatively high dilution with homologous antibacterial serums, but do not precipitate most heterologous antibacterial serums or serums potent in nontype-specific antibodies for the group reactive nucleoprotein P or for the species-specific probable carbohydrate C. Attempts to immunize rabbits with the type-specific protein have been unsuccessful, with simple salt solution extracts of streptococci as well as with purified solutions. This protein seems, therefore, to have the characteristics of a hapten. The type-specific substance (M) is contrasted with the so-called nucleoprotein (P) which shows group relationships with nucleoproteins of related species and is the only fraction of hemolytic streptococcus extracts so far obtained which, after separation from the bacterial cell, is a true antigen leading to the production of antibodies when injected into rabbits. The occurrence of another nontype-specific protein (Y) is suggested by occasional cross-reactions of purified M with certain antibacterial serums. Since it has not been separated from extracts containing the type-specific M, little is known of it either chemically or serologically. The cross-section disappears on tryptic or peptic digestion of the extract. The fact that such extracts do not show cross-reactions with antipneumococcus serums is evidence that this nontype-specific protein is not pneumococcic.

AUTHOR'S SUMMARY.

THE ANTIGENIC COMPLEX OF STREPTOCOCCUS HEMOLYTICUS. REBECCA C. LANCEFIELD, J. Exper. Med. **47**:481, 1928.

The chemical and immunologic characteristics of the species-specific substance (C) of *Streptococcus hemolyticus* are considered. It seems to be a carbohydrate, because considerably purified preparations of C resisted prolonged tryptic and peptic digestion and were negative for the ordinary protein color tests but gave positive Molisch reactions to the limit of the precipitin titer. One such "purified" lot, however, had 4.2 per cent nitrogen and only 28 per cent reducing sugars on hydrolysis. Whether the nitrogen was due to impurities or was combined in the C substance itself, as is true of the type I pneumococcus specific polysaccharide, cannot be stated without more material. The C substance forms precipitates with antibacterial serums prepared against heterologous, as well as against homologous, hemolytic streptococci. These precipitates are typical disks like those formed by type-specific carbohydrates of other species of bacteria. C does not precipitate antinucleoprotein serums. While there is only slight direct evidence that the C substance is not antigenic, there is considerable indirect proof that this is the case. It probably is a hapten in the sense of Landsteiner. A discussion is included of the chemical and immunologic relationships of all the serologically active substances so far identified in extracts of the hemolytic streptococcus.

AUTHOR'S SUMMARY.

THE PROTEINS OF EGG-WHITE AND THEIR RELATIONSHIP TO THE BLOOD PROTEINS OF THE DOMESTIC FOWL AS DETERMINED BY THE PRECIPITIN REACTION. L. HEKTOEN and A. G. COLE, J. Infect. Dis. **42**:1, 1928.

Egg-white contains five distinct antigens, namely, ovoglobulin, ovomucin, crystallizable ovalbumin, noncrystallizable conalbumin and ovomucoid. Ovalbumin, ovomucin and ovomucoid may be completely freed from the other proteins present in egg-white. The preparations of ovoglobulin used were contaminated with ovomucin and probably with a slight amount of ovalbumin.

Antiserums against ovalbumin, ovoglobulin, ovomucin and ovomucoid give no reactions when tested with solutions of fibrinogen, euglobulin or albumin prepared from the blood plasma of the fowl. An antiserum against the whole egg-white reacts with the blood albumin and gives no reaction with the other blood proteins. It has been shown by fractionating the albumin in egg-white, that this reaction is

due to the presence in egg-white of the noncrystallizable conalbumin. The conalbumin and the blood albumin are therefore immunologically, and probably chemically, identical.

It has been found possible to separate conalbumin completely from ovalbumin and ovomucoid. Since, however, an immune serum against blood albumin contains a specific precipitin for conalbumin, such a serum may be used to test for conalbumin in the various protein fractions of egg-white.

AUTHORS' SUMMARY.

SKIN REACTIONS IN RHEUMATIC FEVER. ALBERT D. KAISER, J. Infect. Dis. **42**: 25, 1928.

Eight hundred children from 1 week to 16 years of age were tested intradermally with 0.1 cc. of a 1:100 dilution of the toxic filtrate from cultures of the nonmethemoglobin-forming streptococcus isolated by Birkhaug from cases of rheumatic fever. Approximately 32 per cent of all the children tested reacted positively to the test. Separating children into groups, it was found that 20 per cent were positive when there was no history of rheumatic infection or repeated attracks of sore throat; 35 per cent were positive when there was a history of repeated attacks of sore throat, and 72 per cent were positive when there was a history of rheumatic infection.

There is no parallel reaction with the Schick or the Dick tests.

It is not definitely ascertained whether a positive Birkhaug test indicates a susceptibility to infection with the streptococcus isolated from rheumatic fever, or if it is an allergic phenomenon of a specific nature similar to the tuberculin test.

The results with the Birkhaug test suggest that a positive skin reaction justifies the conclusion that a definite biologic relationship exists between the toxin produced by the nonmethemoglobin-forming streptococcus (Birkhaug) and the hypersensitive state of the skin of persons stigmatized by rheumatic infection. These studies are in complete agreement with Birkhaug's original observations with the toxin isolated by him.

AUTHOR'S SUMMARY.

THE SPECIFIC PRECIPITIN REACTION OF THE MUSCLE HEMOGLOBIN OF THE DOG. LUDVIG HEKTOEN, F. S. ROBSCHEIT-ROBBINS and G. H. WHIPPLE, J. Infect. Dis. **42**:31, 1928.

The results submitted indicate that from the skeletal muscle of the dog solutions of muscle hemoglobin can be obtained that are practically free from blood hemoglobin; furthermore that the hemoglobin of the muscle of the dog gives a specific precipitin reaction which differentiates it sharply from the hemoglobin of the blood of the dog. In connection with this distinction between muscle hemogolbin and blood hemoglobin, it is emphasized as significant that the behavior of the two substances is different on introduction into the blood stream.

AUTHORS' SUMMARY.

STANDARDIZATION OF THE ERYSIPELAS STREPTOCOCCUS ANTITOXIN ON MAN. KONRAD E. BIRKHAUG, J. Infect. Dis. **42**:35, 1928.

A simplified method is devised for the standardization of the erysipelas streptococcus antitoxin on man. Adequate precaution is taken against sensitization to horse serum (globulin) and active immunization against the erysipelas streptococcus toxin. This makes it possible to repeat many series of toxin-antitoxin standardization on the same persons over long periods of time.

AUTHOR'S SUMMARY.

SKIN REACTIONS TO FILTRATES FROM HEMOLYTIC AND ANHEMOLYTIC STREPTOCOCCI, AND B. TYPHOSUS. K. M. HOWELL and M. CORRIGAN, J. Infect. Dis. **42**:149, 1928.

Filtrates of endocarditic strains of streptococcus do not produce skin reactions of sufficient specificity to aid in the diagnosis of subacute bacterial endocarditis.

A high percentage of persons, both healthy and diseased, reacted positively to the hemolytic streptococcus filtrates. There was no apparent correlation between the skin reactions and the etiologic factors of the diseases.

Children susceptible to streptococcus infection give a higher percentage of positive reactions with all streptococcus filtrates than do other children or adults. A positive skin reaction with streptococcus filtrates suggests susceptibility rather than immunity to streptococcus infections.

Positive skin reactions with filtrates of *B. typhosus* apparently indicate immunity to typhoid fever. The tests, therefore, might be useful in determining whether a given person should be artificially immunized against typhoid fever.

AUTHORS' SUMMARY.

SERUM THERAPY OF BOTULISM IN MONKEYS. GAIL M. DACK and WILLARD L. WOOD, J. Infect. Dis. **42**:209, 1928.

Macacus rheus monkeys were found susceptible to the oral administration of small amounts of type A botulinum toxin. About 2,000 MLD (intraperitoneally) for mice was found lethal when fed to monkeys weighing approximately from 2.5 to 4 Kg. The administration of antitoxin after the appearance of symptoms of botulism failed to prevent death. Likewise beneficial effects were not shown when barbital (barbitalum solubile) was given simultaneously. The time of appearance of symptoms and death varied according to the amount of the toxin fed. When small doses were given, the time of appearance of symptoms was much delayed, and the symptoms persisted over a long time. Toxin was demonstrated in the blood of six of nine monkeys after the appearance of symptoms of botulism. No toxin was found in the blood of those monkeys which developed symptoms later than twenty-four hours after they were fed toxin.

The results obtained by feeding botulinum toxin to monkeys are similar to the results that have been reported for botulism in human beings.

AUTHORS' SUMMARY.

SERUM REACTIONS PRODUCED BY FEEDING ANTIGENS. L. P. DOYLE, J. Infect. Dis. **42**:218, 1928.

The observations indicate that small amounts of antibody in the serum of rabbits fed with certain antigens can be detected better by the agglutinin than by precipitin or complement-fixation tests.

In rabbits fed with living cultures of *B. aertrycke* and *B. enteritidis*, specific agglutinins appeared promptly in the blood.

When the cultures were killed in various ways and then fed to rabbits, agglutinins usually did not appear in the blood, although the killed cultures were shown to have agglutinogenic properties when injected subcutaneously.

Cultures of *B. suipestifer* killed with formaldehyde when fed to young pigs produced well defined symptoms of gastric irritation and gave rise to well marked formation of agglutinin.

AUTHOR'S SUMMARY.

RAPID MACROSCOPIC AGGLUTINATION METHOD FOR THE SERUM DIAGNOSIS OF BANG'S ABORTION DISEASE. I. FOREST HUDDLESON and ELIZABETH ABELL, J. Infect. Dis. **42**:242, 1928.

The use of a heated, standardized suspension of *Bacillus abortus* in 12 per cent sodium chloride solution with different amounts of undiluted serum on the glass cover of an especially lighted box affords a rapid macroscopic test for specific agglutinins. The results obtained with this rapid method in several thousand tests indicate that its accuracy and specificity are equal to those of any other method.

AUTHORS' SUMMARY.

A Separation of Phosphorus and Some Inert Protein from the Water-Insoluble Precipitate of Antipneumococcus Serum. Lloyd D. Felton, J. Infect. Dis. **42**:248, 1928.

There has been given the principle of a separation from the crude precipitate, obtained by diluting antipneumococcus serum with water, of a protein essentially free from phosphorus, readily soluble in neutral salts, with a reduction of approximately 30 per cent or more of the protein for a protective dose, and containing most of the protective substance.

Author's Summary.

Febrile Reaction from Intravenous Injection of Protective Substance in Antipneumococcus Serum. Lloyd D. Felton, J. Infect. Dis. **42**:257, 1928.

A discussion of the most likely causes of a pyrogenic reaction following the intravenous injection of the fraction of serum containing the protective substance has been given. It is pointed out that the crude water-insoluble precipitate obtained by diluting antipneumococcus serum with acidulated water is, to a certain extent, pyrogenic. When a fraction containing most of the phosphorus as well as lipins is removed from the crude precipitate, the remaining protein is practically free from this pyrogenic action.

Author's Summary.

Vaccination of Guinea-Pigs Against Tuberculosis with B.C.G. C. Okell and H. J. Parish, Brit. J. Exper. Path. **9**:34, 1928.

The injection of B.C.G. into guinea-pigs did not cause tuberculosis even after intensive courses of five doses of 20 mg. each of the living vaccine. Animals so treated and later inoculated with virulent human and bovine strains of *B. tuberculosis* lived for a significantly longer time than those not previously treated; in one group, infected with a minimal dose of the virulent organisms, complete protection was obtained in 27 per cent of the animals (six of twenty-two). The vaccinated injected animals that died showed typical generalized lesions similar to those injected without previous vaccinations. It is not certain that the protection afforded by B.C.G. is greater than that afforded by various vaccines used in the past.

S. D. Simon.

Attempts to Immunize with B.C.G. Calmette-Guérin. M. D. Arao Imamura and Michihiko Takahashi, Ann. de l'Inst. Pasteur **41**:1330, 1927.

Vaccinated guinea-pigs were subsequently inoculated with virulent tuberculosis bacilli. Positive tuberculin tests resulted in the vaccinated pigs, although dead B.C.G. vaccine did not regularly produce sensitivity. Although vaccinated pigs showed a relatively refractory state to virulent organisms at the site of inoculation, pathologic modifications appeared sooner in vaccinated animals, indicating sensitivity. Immunization in doses of 0.01 mg. and over is "manifestly demonstrated in our experiments."

M. S. Marshall.

Immunity of Guinea-Pigs Against Enteral Infection by the Human Tuberculosis Bacillus After Intragastric Administration of B.C.G. Calmette-Guérin. Kiyoshi Satake, Ann. de l'Inst. Pasteur **41**:1334, 1927.

These experiments show that it is possible to immunize animals against enteral infection with the virulent human tuberculosis bacillus, by treating them first with an appropriate dose of B.C.G., although vaccination with B.C.G. itself gives a negative or weakly positive tuberculin reaction.

Antiheterolysing Serum in a Patient with a Streptococcus Endocarditis. Pasteur Valery-Radot and Jean Stehélin, Le sang **1**:210, 1927.

The authors report a case of a streptococcus septicemia in which the blood serum showed the phenomenon of Neisser and Doering. The serum in this case

inhibited the hemolytic action of normal human serums toward the red cells of an animal of another species and also the hemolysis of an antisheep hemolytic serum. Few cases with a similar pathologic change in the serum have been reported in the literature, and an adequate explanation for its occurrence has not been found.

B. M. FRIED.

BLOOD GROUPINGS; THEORETICAL CONSIDERATIONS; PRACTICAL APPLICATIONS. MAURICE LANG, Le sang **1**:224, 1927.

The article represents a detailed review on the present day knowledge concerning the blood groups and their practical use in the clinic.

B. M. FRIED.

DEATH FOLLOWING TRANSFUSION OF BLOOD. J. FORSSMAN and G. FOGELGREN, Klin. Wchnschr. **6**:1663, 1927.

A man, aged 35, vomited a great deal of blood four hours after resection of the stomach for ulcer. He received blood from a donor presumably of the same group as himself. Later it was found that the donor belonged to group O and the recipient to group A. When the patient had received about 75 cc. of blood, he became pale and pulseless and fainted. The pulse rate remained rapid, and the urine passed during the night was bloody. During the following days, only small amounts of urine were voided. Death took place suddenly on the fifth day after the operation. After death there was marked cloudy swelling of the liver and kidneys; in the liver were numerous fresh necrotic foci, and in the colon were two fresh transverse ulcers. There seemed to be no doubt that death resulted from the transfusion of incompatible blood. Recommendations are made that in testing for transfusions special care be taken to use test serum of proper strength and also to determine directly the relation between the corpuscles and serums of the donor and recipient. It is also urged that the bloodgroups hereafter be designated by letters only.

PAROXYSMAL HEMOGLOBINURIA. ERNST WITEBSKY, Klin. Wchnschr. **7**:20, 1928.

The lytic agent in the serum in paroxysmal hemoglobinuria acts on corpuscles from all the various blood groups without distinction. Serum from severe anemia or paroxysmal hemoglobinuria sometimes but not always may show marked cloudiness after being heated to 55 C. for half an hour.

SPECIFIC REACTIONS AFTER INJECTING SPIROCHAETA PALLIDA INTO MAN. H. KROO and F. O. SCHULTZE, Klin. Wchnschr. **7**:246, 1928.

Thirty-one nonsyphilitic adults were injected repeatedly over an interval with a suspension of killed *Spirochaeta pallida*. Complement-fixation was obtained with the serum and the specific *pallida* antigen, but the Wassermann reaction was persistently negative.

E. F. HIRSCH.

THE DEMONSTRATION OF FOUR HUMAN BLOOD GROUPS BY ISOPRECIPITATION. H. DOLD and R. ROSENBERG, Klin. Wchnschr. **7**:394, 1928.

It is possible to obtain clear extracts with different properties from the stroma of the four human blood groups. The stroma extracts of group O do not give any precipitin reaction with the test serums A and B; those of group A do not react with test serum A, but give a precipitin reaction with test serum B. On the contrary, the stroma extracts of group B react with test serum A, but not with B; those of blood group AB react with both A and B serums. Thus, there is evidence of two separate isoprecipitable substances in the stroma of human erythrocytes, and of two corresponding isoprecipitins in human serums. It is possible also through isoprecipitation to demonstrate the four human blood groups. The stroma extracts are stable for months when stored cool.

AUTHORS' SUMMARY.

ANTIGENIC PROPERTIES OF THE DISTILLATES OF BACTERIAL CULTURES. Z. JERMOLJEWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**:101, 1927.

Various organisms were grown in broth, then killed by heat, allowed to stand for seven to fourteen days and then distilled, after having been mixed with magnesium oxide. In the case of cholera and cholera-like organisms, the distillate contained products which possessed antigenic properties which gave with the serums of immunized animals positive complement-fixation and the Pfeiffer phenomenon. Agglutination and precipitation tests were negative. Immunized animals, in the case of cholera vibrios, survived five times the lethal dose of the corresponding strain, and the serum of immunized animals possessed protective properties. Serums of human beings who had taken the distillate by mouth gave a positive complement-fixation and the Pfeiffer effect with the distillate and with the corresponding bacterial strains. The distillate of the diphtheria bacillus (no. 8) gave a positive complement-fixation reaction.

PAUL R. CANNON.

THE PRESERVATION OF HEMOLYTIC SERUM. W. S. KALININ and S. J. GINSBURG, Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**:112, 1927.

The authors find that 1 per cent of boric acid crystals added to an inactivated hemolytic serum gives a useful method for the preservation of the latter. The titer remains unchanged for a long time; there is no interference with the hemolytic reactions, and the color of the serum remains unchanged.

PAUL R. CANNON.

THE RÔLE OF COMPLEMENT. G. D. BELONOWSKY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**:118, 1927.

Belonowsky concludes that complement favors the union of antigen with antibody, perhaps through the establishment of a uniform and optimal dispersion. The chief portion of the lytic effect is due to the amboceptor, but the presence of complement in all immune processes increases the specific effect.

PAUL R. CANNON.

THE INFLUENCE OF STARCH ON DIPHTHERIA TOXIN. M. P. ISABOLINSKY and W. JUDENITSCH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**:132, 1927.

The authors find that when a starch emulsion of from 40 to 50 per cent is mixed with diphtheria toxin that the toxic effect of the latter in guinea-pigs is much decreased. When they attempted to immunize guinea-pigs with a mixture of starch and diphtheria toxin, however, their results were unsuccessful and indicated that the starch apparently does not adsorb the toxin in the mixture.

PAUL R. CANNON.

THE PRODUCTION OF ARTIFICIAL IMMUNE SERUMS BY THE METHOD OF MEZ AND ZIEGENSPECK. M. EISLER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**:136, 1927.

Eisler attempted to produce artificial immune serums by the method of Mez and Ziegenspeck, using bean and pumpkin seed extracts and utilizing the conglutination and precipitation tests. The reactions were all unspecific, although two widely separated plant species were used. The flocculations observed, he attributes to unspecific colloid reactions.

PAUL R. CANNON.

THE ANTIGENIC ACTION OF BACTERIAL LIPOIDS. M. EISLER and E. EHRLICH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**:151, 1927.

The intravenous injection in rabbits of 80 per cent alcoholic extracts of dried typhoid or cholera bacteria led to neither the formation of agglutinins, bacterio-

lysins nor the heterogenetic sheep blood hemolysin. Such serums, however, contained lipoidantibodies which reacted with the extracts by complement-fixation. The specificity of the latter reaction was not high, a typhoid bacillus extract serum reacting not only with the homologous extract but also with *B. paratyphosus* A and B, *B. coli* and *B. dysenteriae* Flexner, although not with cholera vibrios. The reaction of the cholera serum with the typhoid extract was also negative. The lipoid antiserums did not react with the original bacteria, and the bacteria immune serums of the same organisms did not react with the lipoid extracts.

PAUL R. CANNON.

THE ANTIGENIC FUNCTION OF BACTERIAL LIPOIDS. A. KLOPSTOCK and E. WITEBSKY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**:170, 1927.

The authors succeeded, by immunization of rabbits with killed tubercle bacilli, in obtaining antiserums which gave complement-fixation reactions with both tubercle bacilli and tubercle bacilli lipoids. These serums contained both specific and nonspecific lipoid antibodies. *Proteus X19*, however, formed antibodies only against the original organisms, and not against their alcoholic extracts. The injection into rabbits of alcoholic extracts of both tubercle bacilli and *Proteus X19* bacilli led to the formation of lipoid antibodies.

PAUL R. CANNON.

Tumors

EPIDERMIDALIZATION OF THE CERVIX UTERI AND ITS RELATION TO MALIGNANCY. C. FLUHMANN, Am. J. Obst. & Gynec. **15**:1, 1928.

Fluhmann found epidermidalization in 59 of 1,195 specimens from cases of chronic cervicitis and in 29 of 100 cervical polyps studied by him. Theories as to origin are discussed, and the literature is reviewed. It is the author's opinion that there is not any tangible relationship between epidermidalization and malignancy.

A. J. KOBAK.

A MALIGNANT TUMOR SIMULATING BONE MARROW. SHIELDS WARREN, Am. J. Path. **4**:51, 1928.

A case of an extensive tumor resembling bone marrow, apparently primary either in the pelves of the kidneys or the retroperitoneal fat tissue, is reported in a woman, aged 42, without evidence of leukemic involvement. The possible sources of origin and the nature of this tumor are considered. The name hemocytoblastoma is proposed.

AUTHOR'S SUMMARY.

CONCERNING ECTOPIC CHORIONEPITHELIOMA. REPORT OF TWO CASES. EDMUND DE ZALKA, Am. J. Path. **4**:59, 1928.

Two cases of ectopic chorionepithelioma are reported, one a primary chorionepithelioma of the ovary and the other a growth of the liver. In the case of the ovarian neoplasm no other genital focus existed. Metastatic nodules were found in the skin, lungs, kidneys, liver, pancreas, brain and left temporal bone. After the possibilities as to the origin of ovarian chorionepitheliomas are discussed, this case is believed to fall into the class of ectopic chorionepitheliomas. In the case of the chorionepithelioma of the liver, no primary genital tumor was found, and but few and small metastases were observed in the lungs and in the left kidney; the liver, however, was considerably enlarged and contained huge masses of histologically typical chorionepitheliomatous tissue. Teratomatous elements were not demonstrable. The case is likewise regarded, therefore, as one of ectopic chorionepithelioma, initiated by the transportation in a retrograde manner of chorionic elements through the inferior vena cava.

AUTHOR'S SUMMARY.

THE INCIDENCE AND INHERITABILITY OF SPONTANEOUS TUMORS IN MICE. MAUD SLYE, J. Cancer Research **11**:137, 1927.

In this report, Slye is dealing with the problems of the possibility of cancer being caused by a germ and also with the etiologic relationship between cancer and diet. Observations made in her laboratory for the last eighteen years on about 6,000 spontaneous cancers among 62,000 necropsies, indicate that apparently two essential factors lead to the development of cancer: an inherited local susceptibility to the disease, and a proper irritation applied to the tissue susceptible to cancer. She emphatically states that in every respect the behavior of cancer is inconsistent with the germ theory and also with the diet deficiency theory of cancer. Cancer is not contagious. Spontaneous cancer, in Slye's experience, has seemed to be due to the lack of a mechanism fitted to control proliferation and differentiation in regenerative processes of growth. Those tissues that lack the controlling mechanism proliferate abnormally when regeneration is required of them following irritation or trauma, whereas other tissues proliferate normally in regeneration. Cancer, then, would seem to be a growth process, the result of regeneration which is abnormal because of the lack of a physicochemical mechanism fitted to control proliferation and differentiation.

B. M. FRIED.

A BIOLOGIC MEASURE OF X-RAY DOSAGE. CHARLES PACKARD, J. Cancer Research **11**:212, 1927.

The eggs of the fruit fly *Drosophila* can be used as a dosimeter for estimating the dosage of roentgen ray. Within limits which are discussed, there is a correlation between dosage and effect. Because a large proportion of eggs is normally resistant to roentgen ray, the lethal dose must have a sufficient intensity to kill every individual one in a short time. This is probably true also for those tumor cells which show the same type of variation in sensitiveness to radiations.

AUTHOR'S SUMMARY (B. M. FRIED).

RELATION OF THE PLASMA SODIUM CONTENT OF MICE TO THEIR SUSCEPTIBILITY TO AN INOCULABLE TUMOR. E. E. JONES and M. DOROTHY ROURKE, J. Cancer Research **11**:232, 1927.

The investigation by Jones and Rourke made on white mice brings out the fact that the genetic factors for susceptibility to tumors in this rodent are not expressed in the sodium content of the plasma.

B. M. FRIED.

A CYTOLOGICAL STUDY OF CULTURES IN VITRO OF JENSEN'S RAT SARCOMA. HONOR B. FELL and J. A. ANDREWS, Brit. J. Exper. Path. **8**:413, 1927.

A description of the manner in which the sarcoma was cultured and of where it was obtained is given. In culture, the sarcoma shows two main types of cells which are distinct in structure and behavior. These cells are called fibroblastic and wandering types. In the second division, a description of the cells and their behavior is given. Of the two cells, the wandering type is the most active and motile. These cells also have phagocytic powers. In the third part of the report, the abnormal cells which contain two or more nuclei are described. It is believed that the multinucleated cells are fibroblastic, but their origin is undetermined. These cells have never been seen in living cultures. Another cell which has been noted in these cultures is an epithelioid-like cell believed to be derived from the wandering cell. The conclusion is that the two main types of cells, wandering and fibroblastic, do not have any relationship. Finally, the cytologic changes which take place in the cells proceding death are described.

IRVING SCHROTH.

A Tumor Developed in a Scar of a Cock on Which an Operation Was Performed. H. Bulliard and C. Champy, Bull. de l'Assoc. franç. p. l'étude du cancer **16**:584, 1927.

Bulliard and Champy report the case of a cock which developed a tumor in the operative scar some time after a surgical operation. The authors do not go into details as to the possible genesis of the new growth, which they define as a fusiform cell sarcoma. They describe the presence in the sections of epithelioid cells and also a phagocytosis. They deny the possibility of the tumor being of infectious origin, and outline particularly its development in the scar tissue. The tumor showed metastases to the liver and the lungs.

B. M. Fried.

Concerning Two Cases of Tumor of the Lungs in a Horse and in a Donkey. René Huguenin and J. Surmont, Bull. de l'Assoc. franç. p. l'étude du cancer **16**:593, 1927.

The tumors found by Huguenin and Surmont in a horse and in a donkey are, to all appearances, primary cancers of the lungs. The authors call attention to difficulties in the diagnosis of such tumors, even under the microscope. Analogous to human pulmonary cancer, that of the animal leads to metastases which by their size overshadow the primary lesion, and, as a result, the latter is regarded as being a metastasis. Primary cancer of the lungs was found in practically every domesticated animal.

B. M. Fried.

Dyshematopoiesis and Cancer. Joseph F. Martin, J. Dechaume and H. Ben-Raïs, Bull. de l'Assoc. franç. p. l'étude du cancer **16**:612, 1927.

In a case of a diffuse carcinomatosis of the breast with involvement of the long bones and the bone marrow, the authors found a blood picture typical of splenic anemia; splenomegaly, myelopoiesis and numerous normoblasts in the superficial blood. They deny the possibility of the cancer acting as a hemolytic factor in the production of this type of anemia. In their opinion, the metastases act directly on the area of hematopoiesis by narrowing its field (myelophthisis) and also by their toxins (myelotoxicosis). The hematopoiesis is not arrested, but is hindered and modified. The process is, therefore, not that of anhematopoiesis but that of dyshematopoiesis.

B. M. Fried.

Medicolegal Pathology

Fat Embolism: Report of Two Fatal Cases Following Orthopedic Manipulation. B. E. Clarke, J. A. M. A. **88**:919, 1927.

One woman developed dyspnea three hours after stiff knee and ankle joints were loosened under anesthesia; five hours later she died. Death occurred in a second woman thirteen and one-half hours after similar attempts to correct deformities. The surgical measures were bloodless. The widespread fat embolism which was found included the brain.

Edwin W. Ryerson reported a death from fat embolism following the correction of congenital club feet in an infant, aged 8 months (J. A. M. A. **67**:657, 1916).

E. R. Le Count.

Deaths from Impurities in Ether Used for Anesthesia. S. R. Wilson, Lancet **1**:1117, 1927.

Four anesthesia deaths are reported by Wilson, all in 1926, and during this period similar poisonings which, however, were not fatal occurred in five other patients. All the patients were more or less toxic from disease requiring operation. There were twitchings of the palpebral and other muscles of the face, with

cyanosis shortly after the anesthesia was complete, and then generalized clonic convulsions.

When death followed the convulsions, it came on gradually, with cessation of both the convulsions and breathing. All the patients who died were young, aged from 14 to 21, and in the one body examined the lymphoid tissues were hyperplastic and the thymus enlarged. An examination of the ether was made, and many times the usual amounts of "peroxide" and acetaldehyde found. The poisonings were attributed to these impurities. Some of the other anesthetists in Manchester reported convulsions during this same period, but no deaths.

E. R. Le Count.

Pathologic Anatomy of Acute Carbon Monoxide Poisoning. Francesco Leoncini, Arch. di antrop. crim. **47**:807, 1927.

Differentiation of carbon monoxide poisoning from that of illuminating gas is most difficult. Chemical researches, thus far, have a significance more theoretical than practical. Chemical analysis as well as histopathologic studies does not offer reliable criteria. The diagnosis, as Bergé stated it in 1897, must be based on the study of concomitant circumstances.

Harmful Sequences of Blood Transfusion. H. Bürkle-de la Camp, Arch. f. klin. Chir. **146**:363, 1927.

The dangers of transfusion of blood are infection, especially syphilitic, air embolism and the consequence of failure to type the blood accurately. In the pleural cavities of the bodies of five patients whose deaths were caused by disease for which one or more transfusions had been made, varying amounts of a sanguinolent transudate were found. In one of the bodies a similar fluid was found in the pericardial sac.

In spite of careful typing of the blood for the transfusions, the author states that the transudates in these serous cavities were probabbly caused by slight hemolysis.

E. R. Le Count.

Studies of Acute Alcohol Poisoning. E. Keeser and I. Keeser, Arch. f. Exper. Path. u. Pharmakol. **119**:285, 1927.

Owing to the loss of phosphatids and ketonuria with chronic alcoholism (*Arch. f. exper. Path. u. Pharmakol.* **113**:188, 1926), these investigators suspected that alterations of the ferment action would be found as a consequence of alcohol poisoning. In this second study, four physicians who had a lessened tolerance of 60 cc. drank 110 cc. of absolute alcohol in two and a fifth hours. The alcohol was dilated to 45 per cent concentration. They found in this acute poisoning that there was not any disturbance of protein metabolism, a result previously reported by Feigl, in 1918, for human beings and by Nuzum and Mauer, in 1923, for rabbits.

All these investigators found an increase in residual nitrogen, urea nitrogen and aminonitrogen in the blood in chronic alcoholism. In acute poisoning there is not any increase of indican or acetone bodies in the blood, but from one or two hours after acute intoxication there is a notable diminution of bile pigments with a pathologic increase from nine to ten hours later. The cholesterol in the blood, cholesterol esters, phosphatids and phosphatid-soap fractions are all diminished in acute poisoning. Apparently there is increased activity in the acute intoxications, and a want of lipase in the blood in the chronic intoxications.

The Keesers believe that alcohol does not act directly on the ferments but causes changes in dispersion of colloids when ferments are present, and through such structural disturbances catalysis is promoted. With small doses and acute poisoning they noted increased oxidation and output of carbon dioxide. Using the serum from persons who were acutely intoxicated and buffering the serum to 7.4 p_H, the authors found tributyrin to be more actively hydrolyzed than with

normal serum. The lipases for phosphatids are an exception, for their activity is greater in both acute and chronic poisoning with alcohol.

E. R. Le Count.

Injuries at Birth and the Central Nervous System. A. Dollinger, Ergebn. d. inn. Med. u. Kinderh. **31**:373, 1927.

The subject of this monograph of more than eighty pages, including an extensive bibliography, has important medicolegal relations, because the intracranial hemorrhages in newly born infants, due to trauma at birth, frequently arouse suspicion of infanticide. There are also judicial inquiries regarding the mental and nervous disturbances which follow such injuries. Recognition of the frequency of intracranial injury during birth is one of the remarkable developments in the knowledge of diseases of early infancy during the past decade.

Among the symptoms are convulsions, rigidity of the neck, tetany, yawning, hiccough, vomiting, anomalous sensations and body temperature, symptoms from changes in the vagus, respiratory and vasomotor nerve centers and blood in the spinal fluid. A respiratory stridor is regarded as pathognomonic. Inflammation of the injured brain tissue often occurs, both soon and long after the injury which apparently creates a place of lessened resistance. The prognosis, prophylaxis and therapy are reviewed. Early surgical intervention is advocated, in spite of the high mortality. The author believes that intracranial hemorrhage and injury at birth are responsible for many deaths officially registered under "inanition" or other designations equally indefinite.

Louisa Hemken Bacon.

The Duration of the Action of Alcohol. G. Rosenfeld, Med. Klin. **23**:466, 1927.

The time required by the human body to destroy alcohol so that it is no longer detectable in the blood has been a subject of many investigations. To some degree, an impression has been left by many of the communications regarding this matter that the action of alcohol is at an end when it no longer can be found in the blood. Rosenfeld's objection to this is polemic. He mentions the carefully controlled experiments demonstrating lessened acuity of perception and diminished ability for mathematical reckoning and such manual feats as needle threading, present long after the alcohol has disappeared from the blood.

He repeated Lehmann's production of polychromasia and basophil stippling of the red blood cells of guinea-pigs by alcohol administered subcutaneously or by mouth, and found these persisted for thirty-two days. He also found that alcohol causes a trifold increase of the time required for the heart to return to its normal pulsation after exercise. To these reasons for believing that the action of alcohol is prolonged, he adds the mentality rates reported by Rogers and Porter (no references) who found from statistics of insurance companies in America, Scotland, England and Australia, comprising 6,000,000 insured persons, that for every 100 deaths of abstainers, there were 120 deaths of moderate drinkers, who did not drink each day, and 136 deaths of those who drank daily.

E. R. Le Count.

Harmful Results from Surgical Diathermy. Margrit Schaefer, Schweiz. med. Wchnschr. **57**:268, 1927.

Necrosis produced by the electric current in diathermy and electric amputation of a part of the colon, with postoperative perforation of the stump, caused peritonitis and death of one patient. A second death followed soon after the development of grave cardiac symptoms which appeared during resections of the ribs and plastic work with similar electrical apparatus. A marked cloudy swelling, with fatty changes in the heart and the cardiac collapse are ascribed to be diathermy. In the second patient some fat embolism of the pulmonary capillaries was also present.

The dangers of diathermy and the varying amounts of resistance offered by what the electric current encounters in passing from one electrode to the other are emphasized. In the bowel, for example, air or other gases may intervene, and in any part of the body the current may be much more circuitous and indirect than is indicated by the position of the electrodes and their distance apart.

E. R. Le Count.

Technical

Glycolysis in Blood Samples. A. R. Rose and F. Schattner, Am. J. Physiol. **84**:103, 1928.

In the course of an extended search for antiglycolytic substances suitable for the preservation of blood samples, certain halogen hydrocarbons were found to be most effective. The two best were chlorbenzene and brombenzene, the former used in the proportions of from 0.5 to 4 cc. per hundred cubic centimeters of blood. Iodobenzene and trichlorethylene were somewhat less effective, and these were followed in order by bromtoluene and dichlorbenzene. The antiglycolytic power decreased with increased halogen insertion and with other substitutions. The methane halogen derivatives were not antiglycolytic. Even the halogen compounds which gave the best results did not keep the dextrose within 5 mg. of its initial value. The changes were not constant nor in one direction, and were greatest during the first few days. Plotted against time, they gave characteristic curves which were different for different kinds of blood. Sodium fluoride and thymol did not preserve the dextrose content of sheep's blood, but were effective with most, but not all bloods from human beings. The exceptions did not show any relationship to the occurrence of diabetes.

H. E. Eggers.

The Reliability of the Kolmer-Wassermann Reaction in Pregnancy. Arthur William Stillians, Arch. Dermat. & Syph. **17**:318, 1928.

In a series of 6,954 pregnant women, mostly white, 6 per cent had positive Wassermann reactions. In a series of 814 pregnant negroes, 19.2 per cent had positive Wassermann reactions. The false positive Wassermann reaction occurred in not more than 2.5 per cent of the positive cases in this series — in all probability, much less frequently. False negative reactions, both complement-binding and flocculation, often occur in pregnancy. The flocculation tests are valuable aids in the diagnosis of syphilis in pregnancy. The Wassermann reaction has almost the same diagnostic value in the pregnant as in the nonpregnant woman.

Author's Summary.

Specificity of Kahn Reaction in Febrile Diseases. Jui-Wu Mu and Harthur L. Keim, Arch. Dermat. & Syph. **17**:387, 1928.

The blood of 106 febrile patients — including patients with pneumonia and typhus, relapsing and typhoid fever — was examined by means of the Kahn and the Kolmer-Wassermann reactions. The examinations were made at the height of the fever and repeated in from five to twenty days after the subsidence of the fever. Both reactions gave parallel and specific results. The balance was somewhat in favor of the Kahn reaction, since its results fluctuated least as a result of the fever.

Authors' Summary.

The Relative Diagnostic Value of the Levinson Test and the Glucose Content in Cerebrospinal Fluid. Alfred S. Giordano and Marjorie Ableson, J. Lab. & Clin. Med. **13**:489, 1928.

The percentage of false reactions in the Levinson test is too high to be of positive diagnostic aid in tuberculous meningitis. Low dextrose values are not diagnostic of tuberculous meningitis, even in the absence of pyogenic organisms.

The dextrose content of the cerebrospinal fluid yields valuable diagnostic information when correlated with all possible available clinical data. The chloride content in tuberculous meningitis is less than 700 mg., and not constant in other conditions.

AUTHORS' SUMMARY.

MODIFICATION OF BIELSCHOWSKY'S NERVE-STAIN AS APPLIED TO TUMORS. HORST OERTEL, Canad. M. A. J. **18**:135, 1928.

1. A piece of fresh tissue, not exceeding 1 mm. in thickness, is fixed for at least forty-eight hours in 10 per cent formaldehyde.

2. Wash in distilled water for fifteen minutes, and cut thin frozen sections, floating them on distilled water.

3. Place in pure pyridine for three hours to mordant at 37 C., and wash for one hour in distilled water to remove the odor of the pyridine.

4. Put in a darkly covered bottle of freshly made and filtered 2 per cent silver nitrate solution selected sections, and leave for eighteen hours to impregnate at 37 C.

5. Wash rapidly in distilled water, and transfer for from five to fifteen minutes to the following ammoniacal silver bath: To 5 cc. of 10 per cent silver nitrate add 3 drops of fresh 40 per cent sodium hydroxide, in which a precipitate will form. Decant; wash the precipitate several times and add up to 20 cc. distilled water. Redissolve the precipitate by adding ammonium hydroxide drop by drop, not exceeding 15 drops, and filter through a filter paper previously moistened with distilled water.

6. Wash sections rapidly in distilled water and place in 10 per cent formaldehyde to reduce for ten minutes, or until the white cloud disappears and the sections turn black.

7. It is essential to filter all solutions and baths, to use glass needles, and to agitate sections constantly after step 4. Wash sections well, usually about fifteen minutes, after formaldehyde reduction, and differentiate in a 1 per cent solution of cyanide of potassium for from one to four minutes. (This is an important step.)

8. Wash sections for two minutes in distilled water, and place in a 0.5 per cent solution of gold chloride, to which 3 drops of acetic acid have been added, for ten minutes, or until the sections turn gray.

9. Wash in water for one minute; further reduce in 5 per cent sodium-thiosulphate, wash well again in water and counterstain lightly with hematoxylin.

10. Dehydrate quickly in 95 per cent and absolute alcohol, clear in oil of bergamot and mount from xylol with Canada balsam.

INNERVATION AND TUMOR GROWTH. HORST OERTEL, Canad. M. A. J. **18**:135, 1928.

It has been well established by previous observations that a tumor possesses its own blood supply, and that its vessels are derived from the arteries of its place of origin. Moreover, this vascular construction precedes the actual growth and the extensions of the tumor, primarily by "a local vascular awakening," and subsequently by "a vascular restlessness" at points distant from the tumor. To this must now be added the evidence that the actual tumor is an innervated tissue and stands, therefore, in some relation to the nervous system. Both these observations put the tumor into a somewhat different light from present conceptions, for they indicate that the tumor problem extends beyond the tumor cell to the whole functional and structural complexity of the tumor organization and growth. Indeed, the conception of "independence" and "autonomy" in tumor cells, if these observations are further substantiated, will have to be modified or interpreted accordingly.

AUTHOR'S SUMMARY.

SERO-DIAGNOSIS OF SYPHILIS BY MEINICKE'S MACROREACTION AND MICROREACTION. E. A. RUCKER and L. E. H. WHITBY, Brit. J. Exper. Path. **9**:30, 1928.

The authors report the examination of 254 samples of serums by Meinicke's macroreaction and of 235 by the microreaction; the results were compared with the Wassermann reaction. Ninety-one per cent of the former results were in agreement and 88.5 per cent of the latter, the disagreements being about equally divided between the two possibilities. Analysis revealed that disagreement occurred only in patients who were undergoing treatment. The use of these tests then is best restricted to untreated patients, their distinct value being due to the comparative simplicity and quickness of performance. The microreaction is of particular value in children with congenital syphilis.

S. D. SIMON.

ISOLATION OF TUBERCLE BACILLI ACCORDING TO HOHN, IN ITS PRACTICAL APPLICATION FOR THE BACTERIOLOGIC AND CLINICAL DIAGNOSIS. C. SONNENSCHEIN, Beitr. z. Klin. d. Tuberk. **67**:451, 1927.

The method referred to is a modification of the method by Löwenstein and Sumiyoshi, and has been published in full (*Zentralbl. f. Bakteriol* **98**:460, 1926). Of 183 positive samples of sputum, pus, urine and spinal fluid, 97.27 per cent yielded positive cultures; in 54.64 per cent the tubercle bacilli were found by culture method only and not by microscopic examination. In 2.73 per cent of samples, tubercle bacilli were demonstrated microscopically, but could not be isolated by cultures. The method yielded particularly good results in the examination of pus; in 71.7 per cent of the samples which were microscopically negative, positive cultures were obtained. The earliest appearance of visible colonies occurred in nine days, the latest in thirty-five days.

MAX PINNER.

MICROCHEMICAL DEMONSTRATION OF GOLD IN TISSUES. F. CHRISTELLER, Verhandl. d. deutsch. path. Gesellsch. **22**:173, 1927.

Christeller used stannous chloride for the microchemical demonstration of gold after the injection of sodium aurothiosulphate into men and guinea-pigs. Granules of gold were numerous in the reticular cells and histiocytes, and large scales of gold were present in the lumina of the contorted tubules of the kidney. Granules were found in the tubular epithelial cells, the endothelial cells of the glomeruli and the intertubular connective tissue. The kidney excretes and stores the gold. In the large bowel which also excretes gold, it was found in the interstitial tissue between Lieberkuehn's glands and in the submucosa. Further, it was present in the reticulum cells of the alveoli of the lung, in the pulp cells of the spleen, in Kupffer's cells of the liver and in lymph nodes. In the organism of tuberculosis the distribution was different. Gold was found most frequently in tuberculous organs — not in the tuberculous tissue but in the reticulum of the healthy tissue. Sodium aurothiosulphate is reduced in the organism to gold and may be the cause of gold poisoning. Gold is more markedly retained in the organism of tuberculosis than in the normal one. In the human body, gold was mainly stored in the Kupffer's cells. There was not any difference, however, in the distribution of the gold in the different organs of tuberculous and healthy persons.

WILLIAM C. HUEPER.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Feb. 13, 1928

DALLAS B. PHEMISTER, *President, in the Chair*

RHINOSCLEROMA OF THE LARYNX AND PHARYNX IN TWO IMMIGRANTS. S. M. CROWE. The John Jay Borland Fellow in Medicine. (From the Norman Bridge Pathological Laboratory of the Rush Medical College of the University of Chicago and the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago.)

Rhinoscleroma, a chronic granuloma of the upper respiratory passages, is common in Europe. Although it is not common in the United States, it should be considered as a possible explanation of chronic diseases of the pharynx or larynx, especially in foreigners.

Watkins (*Surg. Gynec. Obst.* **33**:47, 1921), in a report of rhinoscleroma of the larynx, gives a careful review of the disease. The condition, according to Askanazy (in Aschoff, L.: Pathologische Anatomie, Jena, Gustav Fischer, 1923, vol. 1, pp. 154-156), occurs frequently in East Prussia, Silesia, Austria, Bohemia and Hungary, less often in Russia and the Walliser Alps, Italy and Central America, and infrequently in Western Germany and France. As evidence of the rarity of the disease in the United States, Watkins says that of a million and a half patients treated during thirty years at the Johns Hopkins Hospital, only two had rhinoscleroma. Nearly all patients with the disease in this country have been immigrants. The condition is said to occur in persons from 15 to 40 years old (Ormsby, O. S.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1921, pp. 655-657), and especially in those of the poorer classes (Beitzke, H., in Aschoff, L.: Pathologische Anatomie, 1923, vol. 2, p. 259).

There is some difference of opinion as to the relationship of the Bacillus of Frisch to rhinoscleroma. Babes (in Kolle-Wassermann: Handbuch der Pathogenen Mikroorganismen, Jena, Gustav Fischer, 1913, pp. 1237-1254) considers its specificity not absolutely proved. Bailey (*J. Cutan. Dis.* **37**:447, 1919), however, thinks the bacillus is the etiologic factor in the disease, and Quast (*Centralbl. f. Bakteriol.* **97**:174, 1925) believes it must be granted an important rôle.

Rhinoscleroma may start in the nasopharynx or larynx, according to Kaufmann (Lehrbuch der speziellen pathologischen Anatomie, Berlin and Leipzig, Walter de Gruyter & Company, 1922, vol. 1, pp. 228-229), and spread from there as painless nodules of characteristic hardness to the skin of the nose and upper lip, to the palate, and even to the lining of the trachea and bronchi (Beitzke). Frequently a coryza of long standing (Toeplitz, M., and Kreuder, H.: *Am. J. M. Sc.* **130**:81, 1905) has preceded the onset of nasal obstruction, sometimes with epistaxis (Watkins). The disease is chronic and, according to Babes, swellings of twenty years' duration are not infrequent. The general health is usually not affected although emaciation may result from interference with swallowing and breathing. Growth into the lumen of the air passages may cause death from suffocation and the likelihood of obstruction may be increased by contractions of scar tissue.

Beitzke describes the scleroma tissue as flat or swollen tumors of connective tissue that are as hard as cartilage. They grow slowly and have a slight tendency to necrosis. The new nodules consist of plasma cells, vascular connective tissue, and large vesicular cells known as Mikulicz's cells which fre-

quently contain bacilli, while the old nodules are compact sclerotic connective tissue. Babes derives the Mikulicz' cells from the plasma cells, and the hyaline bodies, also common in the tissue, he derives from these cells as well as from red blood cells phagocytized by endothelial cells and from hyaline changes in the fused capsules of the bacilli.

Watkins considers the microscopic study of a piece of the tissue the only certain method of identifying the lesions, but mentions as factors favoring the diagnosis of scleroma the chronicity, the absence of tissue destruction and pain, the ivory-hardness of the lesion, and the European nationality of the patient. Elbert, Feldmann, and Gerkes (*Centralbl. f. Bakteriol.* **101**:384, 1927) consider the complement-fixation reaction of great value, especially in the recognition of early or latent rhinoscleroma.

In 1903, Dr. D. W. Gray reported before this Society a Bohemian patient of Dr. E. L. Kenyon's with nasal symptoms of six years' duration. The rhinoscleroma bacillus was isolated in pure culture and was demonstrated in tissue from the lesions. My report concerns the tissues from two patients, the pharynx and larynx of one and the larynx of the other. Both patients died of respiratory obstruction caused by rhinoscleroma.

Case 1.—J. K., a Polish laborer, aged 30, was admitted to the service of Dr. Friedbergh at the Cook County Hospital in September, 1912, with a history of difficulty in breathing for a year, which became worse the six weeks before admission. In one attack an operation on the larynx had resulted in some improvement. There was no history of syphilis. The patient was emaciated, acutely ill, and unable to speak except in a whisper. Laryngoscopic examination was unsatisfactory as he could open his mouth only about half an inch. The breath was foul. His breathing continued to be difficult and in about twelve hours, just after a low tracheotomy had been performed, he died. The clinical diagnosis was syphilitic laryngitis. The anatomic diagnosis at the postmortem examination made nine hours later (E. R. LeCount) was: Chronic indurative pharyngitis (rhinoscleroma) with marked pharyngeal stenosis; ancient tracheotomy scar; recent low tracheotomy wound; emaciation; passive hyperemia of the lungs; chronic diffuse nephritis; general passive hyperemia of all the abdominal viscera; bilateral fibrous pleuritis; fibrous adhesions between the liver and the diaphragm and about the appendix vermiformis. Careful examination of the body during the postmortem examination did not disclose syphilis.

The tissue preserved in formaldehyde had a funnel-shaped pharynx about 4 cm. long and was rigid with fibrous tissue about 5 mm. thick. The large end above was not over 2 cm. in diameter, and the lower end, the opening into the larynx and esophagus, was a slit. The epiglottis was sharply curved and was embedded in the lymphoid tissue at the base of the tongue, lying in the front two thirds of a hard fibrous ring about 9 mm. in diameter.

Histology.—In microscopic preparations the thickened wall of the pharynx was made up of heavy bands of fibrous tissue with intervening masses of lymphocytes and plasma cells, and these two layers, each about 0.5 mm. thick, alternated.

Case 2.—E. C., a laborer, aged 35, came to this country from Italy at the age of 7 years and again at 11, and according to his physician, Dr. Otto Kahn, the patient had been hoarse for fifteen years. He had had syphilis in 1915, but repeated treatments with mercury and arsenic had not improved his voice. His wife thought the hoarseness had increased during the past two years and was aggravated by drinking. The larynx had never been examined. There had been a slight cough the last two years, but no noticeable difficulty in breathing until two days before his death, when the man choked while at work. He seemed well at home that evening. Finally he had a fainting spell at work and was unable to breathe. He was blue when taken to the physician's office and died on the way to the hospital. The essential items of the anatomic diagnosis from the postmortem examination (Edwin F. Hirsch) April 20, 1927, about eighteen hours after death were: rhinoscleroma of the larynx with marked

stenosis; marked acute emphysema of the lungs; marked edema and hyperemia of the lungs; hyperplasia of the lymphoid tissue at the base of the tongue; scar of the glans penis; scar of the lining of the aorta; fatty changes of the lining of the aorta and coronary arteries.

The mucosa of the larynx was markedly thickened from the level of the aditus to that of the vocal cords, especially in the vestibule, where there was a triangular puffy swelling about 15 mm. wide at the base along each aryepiglottic fold, the apexes directed medially so that the swellings were in apposition across the midline. These swellings were about 5 mm. in maximum thickness. In the mucosa, just anterior to the interarytenoid notch, was an irregular, elevated mass about 1 cm. in diameter and 5 mm. thick. Between the mass and the swelling in the vestibule two thick folds projected touching each other across the midline and completely closing the lumen of the larynx. Beneath were other smaller folds, two of which were the thickened ventricular folds closing over the glottis and making it difficult to see the vocal cords. The

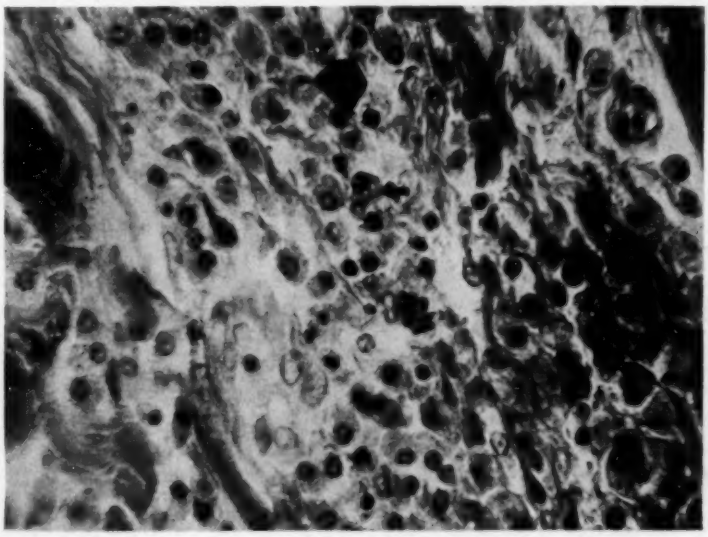


Fig. 1.—Section of the rhinoscleroma tissue; × 590. There are many plasma cells and lymphocytes and two clusters of hyaline bodies. Phosphotunstic-acid hematoxylin stain.

larynx was opened by a median cut along the posterior wall. The opening of the glottis was firmly closed by the thickened vocal cords.

Histology.—In sections from two places in the larynx the stratified squamous epithelium was intact; beneath it was a coarse meshwork of collagenic fibrous tissue, and between the meshes were many plasma cells and lymphocytes with a few leukocytes and mast cells. There were occasional large cells with finely lined cytoplasm and small dark nuclei, Mikulicz cells. In cells similar to these and in plasma cells and free in the tissue spaces were hyaline bodies varying from the size of a plasma cell to smaller than a red blood cell, sometimes singly and sometimes in clumps (fig. 1). The cellular layer was from 1 to 2 mm. thick. Beneath it was dense vascular wavy fibrous tissue with many plasma cells and lymphocytes. The fibrous tissue extended into the muscle in thick bands between the shrunken fibers. In some crevices in the epithelium as well as in some of the ducts of the many mucous glands in the sections

were masses of short, thick, gram-negative bacilli, but none were found anywhere in the deeper layers of the tissue.

Rhinoscleroma was not suspected during life in either patient, nor was the rhinoscleroma bacillus ever demonstrated. Both patients were foreigners, and one had been in this country for twenty-four years. In one, symptoms had been present at least a year, in the other for fifteen years. One died of respiratory obstruction after rather rapid aggravation of the condition when otherwise he was apparently well; the other, after a more prolonged period of difficult respiration and emaciation.

DISCUSSION

P. CANNON: What recent literature is there on immunologic tests for the specificity of the Bacillus of Frisch?

B. C. CROWELL: How are the lesions of the second patient differentiated from syphilis?

R. H. JAFFÉ: Lesions like those in the larynx and pharynx occur around the bronchi. Were these noted?

S. M. CROWE: Positive complement-fixation tests with the patient's serum are reported. The presence of Mickulicz' cells and hyaline bodies are distinctive in the lesions of the second patient. No lesions were found along the bronchi.

CHICKEN-BONE PERFORATION OF THE ESOPHAGUS WITH BACTERIAL EROSION OF A LEFT BRONCHIAL ARTERY. E. O. LATIMER and J. D. WILLEMS.

The complete report will be published in the ARCHIVES OF PATHOLOGY.

MYCOTIC SPLENOMEGALY (TYPE GANDY-NANTA). R. H. JAFFÉ and L. R. HILL.

The complete report will be published in the ARCHIVES OF PATHOLOGY.

GLYCERINE PRESERVATION OF SEROLOGIC TEST MATERIALS, AND THE INFLUENCE OF HEAT ON GLYCERINATED WASSERMANN POSITIVE SERUMS. H. R. FISHBACK and FRANCES PERSTEIN.

Glycerine is used for preserving serums for Wassermann and other complement-fixation tests, and for tests involving agglutinins, precipitins and lysins. It is also used commonly in Wassermann amboceptor. It can be used in preserving spinal fluids for the Lange test and may be added to certain colloidal solutions used in serologic work without injuring the reactive qualities.

A series of tests was run with prolonged heating of Wassermann-positive serums (inactivated for thirty minutes at 56 C. and preserved by the addition of glycerine to 50 per cent strength) to determine the effect of heat on the Wassermann reagin and on the anticomplementary factor. The samples of serum were divided into a number of portions and each portion was subjected to a Wassermann titration test after varying periods of heating.

Many serums had little or no anticomplementary activity. In others, the anticomplementary factor was heat-resistant, but could be removed by titrating with small amounts of serum.

The Wassermann reagin withstood prolonged heating in the glycerinated serums, in one serum a four plus Wassermann resulted with 0.045 cc. of serum after twenty-two hours of heating at 56 C.

DISCUSSION

E. R. LONG: Many years ago, Robert Koch preserved tuberculin with glycerol. If glycerol were present from 5 to 20 per cent, the tuberculin resisted heating. Dr. Seibert and I have had a similar experience and think probably some stable compound is formed.

CONCEALED PRIMARY CARCINOMA OF THE PALATINE TONSIL. FRANK M. COCHEMS. (From the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago.)

It seems that reports of primary carcinoma of the palatine tonsil recording the results of postmortem examinations are rare, although those determined by clinical observation and study are not uncommon. Of the antemortem diagnoses, in 1906, Meller (*Deutsche Ztschr. f. Chir.* **84**:105, 1906) cited twenty-nine; from 1884 to 1909, Wood (*Penn. M. J.* **12**:431, 1909) found sixty-four; in 1904, Linderborn (*Beitr. f. klin. Chir.* **43**:569, 1904) reported five cases and cited eighty reported by Mikulicz, Stappert, Pierin, Kronlein and Czerny; and Ross (*Laryngoscope* **35**:15, 1925) found twenty recorded between 1910 and 1925. In 1919, McCoy (*Laryngoscope* **29**:422, 1919) reported four cases, Canuyt (*Rev. d'laryng.* **39**:12, 1918) one, Rice (*J. Ophth. Otol. & Laryngol.* **25**:96, 1921) one, and Janeway (*Am. J. Roentgenol.* **7**:92, 1920) one. In 1914, Smith (*New York State J. Med.* **24**:289, 1924) reported forty patients, and in 1927, Quick and Cutler (*Surg. Gynec. Obst.* **45**:320, 1927) ten.

Of the reports containing accounts of postmortem examinations, there are seven by Meller (*Deutsche Ztschr. f. Chir.* **84**:105, 1906) and one by Moncary and Cornil (*Bull. et mém. Soc. anat. de Paris* **20**:180, 1923). Metastases were mentioned in the submaxillary, cervical, supraclavicular, mediastinal and abdominal lymph nodes, but none in the liver.

CASE 1.—J. F., a white man, aged 57, a shoe-maker, entered St. Luke's Hospital on Feb. 12, 1927, complaining of inability to eat solid foods, a loss of 15 pounds (6.8 Kg.) of weight, an abdominal tumor with pain and tenderness in the epigastrium and under the left costal border, all of two months' duration. In the notes of the physical examination the following were mentioned: a marked edema of the ankles, enlarged and firm lymph nodes of the anterior and posterior left cervical region; a large, smooth, protruding mass in the epigastrium extending from the ensiform cartilage to 2 inches above the navel. A lymph node removed from the neck contained masses of cells like pavement epithelium, and a diagnosis of metastatic squamous cell carcinoma was made. The primary site of the carcinoma was not determined clinically. About one month after admission, the patient died.

The postmortem examination (Edwin F. Hirsch) was made seventy-four hours after death. The trunk, head and neck were examined, and the essential portion of the anatomic diagnosis was: cryptic primary carcinoma of the left tonsil; metastatic carcinoma of the left cervical, mediastinal, retroperitoneal and pancreatic lymph nodes and of the liver; marked emaciation.

The left cervical lymph nodes behind the sternocleido-mastoid muscle from the tip of the mastoid bone downward were markedly enlarged and formed a mass of tissue 10 cm. long, 5.5 cm. wide and 3 cm. thick. On surfaces made by cutting, these contained white tissue in nodules streaked with yellow, and a few were necrotic.

On the left side of the soft palate, 1 cm. in front of the posterior edge and extending to within 1 cm. of the midline, was a roughened place in the mucosa 2 to 3 cm. in its greatest dimension. It occupied the region of the left tonsil. On the right side was a little shrunken tonsil tissue. There were no noteworthy changes in the tissues at the root of the tongue, the larynx, the upper part of the esophagus and nasopharynx, and the thyroid gland except as mentioned. The right cervical lymph nodes were not enlarged.

In the region of the thymus was a mass of lymph nodes 4 by 4 by 3 cm. and in front of the pericardium, a slightly smaller mass of tumor tissue. The thoracic peri-aortic lymph nodes were firm, gray masses up to 1 cm. in diameter as were those at the level of the receptaculum chyli. The lymph nodes at the bifurcation of the trachea were small and black. The left renal and suprarenal veins were surrounded and embedded in a mass of soft, gray-white lymph nodes lying chiefly in front and to the left of the inferior vena cava and on

surfaces made by cutting they were found to contain soft, gray-white-pink tissue with small regions of necrosis.

Along the upper border of the head of the pancreas and pushing away the lobulated pancreatic tissue was a soft, white-yellow mass that extended across the duct behind, and was continuous above the pancreas and to the left with a mass of similar soft, easily crushed and friable tissue in the region of the biliary lymph nodes.

The liver weighs 5,050 Gm. and about 50 per cent of the outside was studded with from 80 to 100 soft, gray-white nodules, some umbilicated, ranging from 1 to 9 cm. in diameter. On surfaces made by cutting the nodules there was soft, white tissue and regions of yellow up to 0.7 cm. in diameter and the centers were necrotic and soft. Between the nodules, the lobular markings of the liver were distinct, their peripheries raised and yellow and the tissue about the central veins dark red and depressed.

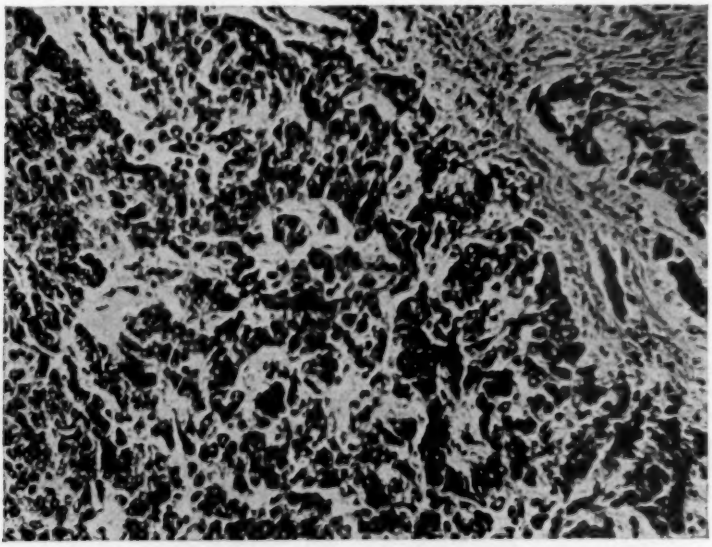


Fig. 2.—Tumor growth in the left tonsil; × 153.

Histology.—The histologic preparations from the left tonsil region (figs. 2 and 3) were composed of about 30 per cent of lymphoid tissue and 65 per cent of ingrown masses of stratified epithelium, the cells small like those of the deeper layers. The remainder was fibrous tissue and fragments of a stratified squamous surface epithelium, regular in some places but in others, especially in the crypts, continuous with the ingrown masses of stratified squamous epithelium. The sections from the mass of lymph nodes along the left sternocleidomastoid muscle were almost entirely tumor tissue similar to that described in the left tonsil. There were irregular regions of necrosis in these sections as large as 1.4 mm. in diameter, more marked in some places than in others. In the sections from the mediastinal and retroperitoneal tissues and the liver were more of these stratified squamous cell masses.

The noteworthy features in this patient were the extensive metastases into the left cervical, mediastinal, retroperitoneal and pancreatic lymph nodes and into the liver from a small hidden primary circinoma of the tonsil. Histologically, it was of the stratified squamous cell type without hornification. An

interesting feature was that, while the primary site was not determined before death, the report of the examination of a cervical lymph node taken during life suggested that the site of origin was in a stratified squamous epithelial surface.

CASE 2.—A. H., a colored laborer, aged 67, entered St. Luke's Hospital on April 13, 1927, complaining of pain in the left side of the throat of one and a half year's duration and "something growing in his throat" for the past three months. There was a fungoid, ragged mass on the left side of the pharynx that extended medially to the uvula. On May 3, he developed symptoms of mechanical intestinal obstruction and on May 5, an enterostomy was performed. He died on May 7.

The postmortem examination (Edwin F. Hirsch) was made nine hours after death. The neck and trunk were examined, and the essential portion of the anatomic diagnosis was: primary carcinoma of the left tonsil; secondary carcinoma of the left wall of the pharynx; emaciation; fibrous tissue adhesions

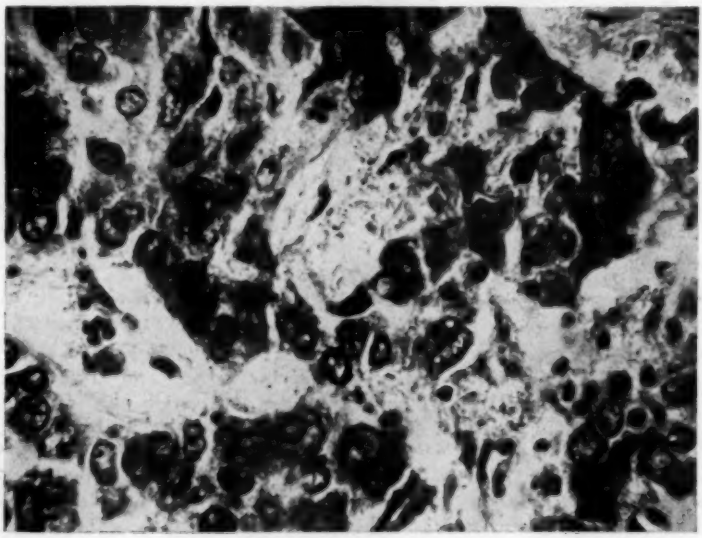


Fig. 3.—Absence of hornification; × 498.

about the splenic flexure of the colon with obstruction of the lumen of the bowel; recent enterostomy wound.

On the left side of the pharynx occupying the region of the tonsil extending medially in the soft palate to the uvular and anteriorly 1 cm. from the posterior margin was soft, necrotic, green-yellow tissue. This mass reached down the left wall of the pharynx into the angle between the epiglottis and base of the tongue. The cervical lymph glands were not enlarged. The peri-aortic and peribronchial lymph nodes were not enlarged. There were a few small, thin-walled abscesses in the left lung.

Histology.—About 30 per cent of the sections from the left tonsil were composed of ingrown epithelial tissue, chiefly in irregular masses as large as 0.5 mm. in diameter. There was only a little lymphoid tissue remaining, the tonsil proper being chiefly dense fibrous tissue in which there were focal regions of chronic inflammation. Along one edge of some of the sections was a layer of stratified squamous epithelium continuous with the ingrown masses. The centers of some of the epithelial masses were necrotic, while in others were dense concentric whorls of hornified, flattened cells as large as 0.15 mm. in

diameter. In portions of the sections of the soft palate and left pharyngo-epiglottis fold were ingrown masses of stratified squamous epithelial cells similar to those in the left tonsil. The sections from the styloid process of the left temporal bone consisted of a small mass of bone surrounded by a layer of dense fibrous tissue and in this fibrous tissue, moderately well demarcated, were a few small masses of stratified squamous epithelium as large as 0.2 mm. in diameter. Sections of the right tonsil were free from tumor tissue as were those of the cervical and mediastinal lymph nodes.

Ross (*Laryngoscope* **35**:15, 1925) proposes that the site of origin of the carcinoma is at the junction of the epithelial surface of the tonsil and the pillar (as with a mucocutaneous junction), but adds that it is difficult to establish such a hypothesis because the reports of carcinoma of the tonsil usually deal with new growths of considerable standing. In the two patients whose cases are here reported, the difference in the dissemination of the metastases seemed to depend on whether the tumor started on the surface of the tonsil or in a crypt. In the first instance, the carcinoma probably arose in a crypt of a tonsil with only slight fibrous change, and there were extensive metastases in the left cervical, mediastinal, retroperitoneal and pancreatic lymph nodes and in the liver. In the second instance, however, the tumor probably arose on the surface of a tonsil containing much fibrous tissue and having a poor lymphatic drainage, so that the spread was entirely by direct extension, except the small metastasis in the region of the styloid process of the left temporal bone. Quick believes that the extension to the cervical lymph nodes is embolic. It follows that in a patient with markedly scarred tonsils and a poor lymphatic drainage; the metastatic involvement of the cervical lymph nodes is delayed.

Metastatic growth of carcinoma of the tonsil in the cervical lymph nodes is usually unilateral, probably owing to the lymphatic drainage as mentioned by Warren (*Ann. Surg.* **48**:481, 1908) and in this respect it differs from carcinoma of the nasopharynx, which according to Gatewood (*J. A. M. A.* **66**:499, 1916) is bilateral. Meller (*Deutsche Ztschr. f. Chir.* **84**:105, 1906) believes that when there is bilateral involvement of the cervical lymph nodes with carcinoma of a tonsil an obstruction of the lymphatics on the side of the tumor has caused the lymph to drain into the opposite side with the development of metastases there.

Smith (*New York State J. Med.* **24**:289, 1924) concludes from the biopsy examination of forty patients with epithelioma of the tonsil that pearly formation is rare and in his material found it but once. Quick and Cutler (*Brit. J. Radiol.* **32**:329, 1927) believe that hornification, spines and pearl formation are regularly absent. Of the two instances of carcinoma of the tonsil here reported, it was present in one.

Regular Monthly Meeting, March 12, 1928

DALLAS B. PHEMISTER, *President, in the Chair*

THE EFFECT OF PEPTONE ON THE HEPATIC VEINS IN THE DOG. J. P. SIMONDS and W. W. BRANDES. (From the Department of Pathology, Northwestern University Medical School, Chicago.)

A means of mechanically recording the outflow from and simultaneous alterations in the volume of a perfused liver of a dog was described. The perfusion fluid consisted of well oxygenated, diluted, defibrinated blood from the same animal whose liver was being perfused. With this mechanical device, it was shown, that when peptone is injected with the perfusion fluid entering the liver by the portal vein, there is a decrease in outflow and an increase in volume of the liver, and that when peptone is injected with the perfusion fluid entering by way of the hepatic vein there is a decrease both in outflow

and in the volume of the liver. Uniform results were obtained with the livers of eight dogs. The conclusion seems warranted that peptone causes a constriction of the hepatic veins in the dog.

DISCUSSION

DR. B. HALPERT: What difference in pressure is there between the hepatic and the portal veins.

DR. SIMONDS: About 30 to 40 mm. of mercury.

BLOOD SUGAR CHANGES FOLLOWING INJECTIONS OF PEPTONE IN THE DOG. W. W. BRANDES and J. P. SIMONDS. (From the Department of Pathology, Northwestern University Medical School, Chicago.)

The experiments indicate that peptone causes a hypoglycemia during the period when the blood pressure is low and the liver engorged and tense. When the blood pressure rises and the liver becomes less tense, a rather marked rise in the blood sugar occurs.

At the time of peptone shock in the dog when the liver has reached its greatest size and is most markedly engorged with blood, there is a great increase in the sugar content of the blood from the hepatic vein, while at the same time there is a decrease in that of blood from the femoral vein.

As long as the liver is free and unimpeded, there is no marked difference in the sugar values of the blood from the hepatic and femoral veins. In peptone shock, the obstruction to the free flow of blood through the liver with the attendant congestion and local stasis appears to cause an increased glycogenolysis in the liver. During the height of peptone shock, so little blood leaves the liver that, although the sugar content of such blood is high, the normal blood sugar level of the general circulation cannot be maintained and a hypoglycemia results. As the obstruction is relaxed during recovery, the increased sugar in the liver enters the general circulation and causes hyperglycemia.

NEW MEDIUMS FOR THE CULTURE OF TUBERCLE BACILLI. H. C. SWEANY and MAX EVENOFF. (From the Research Laboratory of the Municipal Tuberculosis Sanitarium, Chicago.)

Continuing the work recently reported (*Am. Rev. Tuberc.* **17**:47, 1928) we have arrived at a method that seems to give consistent results in the culturing of tubercle bacilli from contaminated material.

We reported in a footnote of that article that a combination of milk with egg medium gave almost perfect results. The present work includes our studies on this new medium with various modifications, and the addition of other ingredients that seem to enhance the growth of the tubercle bacillus. The work may be divided into three parts: culture medium, preparations of specimens and technic of inoculation.

The two culture mediums of importance resulting from the work may be termed the "milk" and the "cream" medium. Other ingredients such as potato extract were without added value. The milk medium is prepared by leaching the veal in the Petroff method with sterile fresh milk instead of water. The milk is sterilized in the Arnold sterilizer on two successive days for forty-five minutes. After the milk infusion has been squeezed out, a double quantity of eggs is added and enough glycerin to make 5 per cent.

The cream medium is prepared by using a little less milk than in the previous method and by adding sufficient sterile cream to make the final volume of the cream 10 per cent. No glycerin is added. For example, if the milk infusion is 500 cc. it will be necessary to add 150 cc. of cream and enough eggs to make 1500 cc. The greatest care must be exercised in cleaning and sterilizing the utensils and materials used and in keeping out all dirt or dust

liable to contain spore-forming organisms. The medium is then incubated three days in the incubator and three days at room temperature. This brings out contaminations and dries up the water of condensation.

The treatment of the suspected material is important. In spite of the favorable results of Loewenstein, Corper and others with the acid treatment, we have had better results with 3 per cent sodium hydroxide added to an equal quantity of material making a final volume of 1.5 per cent of sodium hydroxide. The material is mixed well with the sodium hydroxide and placed directly in the centrifuge and sedimented long enough to make the total time of exposure twenty minutes. The supernatant liquid is poured off and the drops allowed to drain. This sediment free from mucus is then neutralized and planted on the medium. It is important to reduce the sediment to as small a bulk as possible and spread thin on the medium. This permits the surface to become dry and affords an environment best suited for growing the acid fast bacilli and least suited for contaminations and degeneration forms.

Should a contamination arise, the tube should not be discarded unless the medium is liquefied, for generally the contamination will be overgrown by the tubercle bacilli. After a growth has been procured, the organisms can be freed of contamination if desirable. We have obtained over 90 per cent growth with less than 15 per cent contamination by this system of procedure.

DISCUSSION

DR. L. E. DAY: Can you grow the bovine type?

DR. SWEANEY: This has not been tried. So rarely do we find the bovine type, that it is a curiosity.

DR. LONG: Tubercle bacilli are difficult to isolate by cultures, but can be easily grown after isolation. The growth may be dependent on vitamins.

A DICEPHALIC MONSTROSITY. DR. FREDERICK H. FALLS. (From the Department of Obstetrics and Gynecology, University of Illinois, College of Medicine, Chicago.

This dicephalic monstrosity was born at the Research Hospital, Nov. 11, 1927. The mother came for examination to the outpatient clinic on April 9, 1927. She was a white, American woman, aged 19, who had been married for six months, and this was her first pregnancy. She last menstruated December 24, and the estimated date of confinement was September 20. Her menstrual history was normal. When a child the patient had had measles and diphtheria, pneumonia at the age of 16, erysipelas just before the pneumonia and influenza in 1918. She said that she did not have venereal disease. Her father died of tuberculosis and her mother of carcinoma of the stomach. She had a twin brother, and one of her cousins had twin babies. There were no twins on the husband's side of the family. Her husband was 21 years of age, normal physically and said that he did not have venereal disease. The early pregnancy was uneventful and a general physical examination did not reveal any abnormality. Abdominal palpation revealed two heads. However, only one set of heart tones could be heard. A roentgenogram showed the two heads to be closely associated, and several others taken a few days apart showed two heads and two spinal columns, which maintained the same relationship to each other. On September 7, the patient entered the hospital with vaginal bleeding and some pain in the lower portion of the abdomen. A diagnosis of central placenta praevia was made. The vaginal bleeding continued slightly for forty-eight hours, when a cesarean section was decided on because of the association of a dicephalic monstrosity and a central placenta praevia. By cesarean section, the baby was delivered and it lived forty minutes. The placenta was over the lower portion of the uterine segment. The patient made an uneventful recovery.

The male fetus was 41 cm. long and weighed 2,960 Gm. It had two symmetrical heads fully developed and two necks which fused at the upper portion of the thorax. There were two arms and two legs. The diameters of the fetal heads were:

	Right Head	Left Head
DIAMETERS		
Fronto-occipital	11.0	10.0
Mento-occipital	11.5	11.0
Sub-Bregmatic occipital	10.0	9.5
Bitemporal	7.0	9.5
Biparietal	8.0	9.0
Bisacromial	12.5	
Bisiliac	8.5	
CIRCUMFERENCES		
Fronto-occipital	31.2	31.5
Mento-occipital	32.0	33.0
Sub-Bregmatic occipital	31.0	31.5
Chest	33.0	
Bisacromial	35.5	
Bisiliac	25.0	

The roentgenogram of the monstrosity after delivery showed the spinal columns to be separated down to the sacrum. The right and left clavicles and scapulae appeared normal. In the intervertebral region, there were rudimentary ribs coming off from each spinal column and interdigitating in the midline. The lower extremities seemed normal. The dissection revealed a single heart, normal in size for the term of pregnancy, which measured 5 by 3 by 2.5 cm. The pericardial sac was normal. There were four pleural cavities. The two lateral pleural cavities were about normal in size and contained normal lungs. Median to these were two small cavities about one third the size of a normal full term fetal pleural cavity. The trachea branched at about the usual level, to send a larger branch to the more normal lung and a smaller branch to the rudimentary lung. In the region of the neck there were two thyroid glands of about normal size and shape, and there was an anastomosis of the median external jugular veins. There were two thymic glands of average size; one stomach, which was approximately one half the normal size; one liver, grossly normal, but without a gallbladder; two kidneys of normal size and location; one spleen; and one intestinal tract, apparently normal except for some dilatation of the transverse and descending colon. The spinal columns were normal in size, and the rudimentary ribs interdigitating were found in the space between the spines.

The etiology of these monstrosities is not definitely known. The theory proposed by Newmann to explain their occurrence is that there is a division of the bilateral primordia of a single embryonic axis. Complete isolation results in the formation of single ovum twins. Slighter forms of isolation give rise to the double monsters with varying degrees of duplicity. It is thought that some irritating influences on the ovum in the development of its process may give rise to these anomalous formations. Newman gives three possible retarding factors which may, he assumes, promote the development of twins: (1) under stimulation of the egg due to some defect in the development initiating mechanism in the sperm; (2) belated placentation, due to a failure of the corpus luteum to stimulate the uterine mucosa, and (3) an hereditary recessive gene, growth-retarding in character. In this connection it may be significant that this woman had pneumonia and erysipelas three years before the development of this abnormal fetus, and that she also had influenza nine years before and had had measles and diphtheria as a child. The possible effect of these serious infections on the maturing ova may conceivably have changed its reaction, so that when stimulated by fertilization, an abnormal rather than a normal product resulted. The relationship between monstrosity and the associated placenta praevia is also of interest. This is the second instance of this coincidence that I have seen. Greenhill has said that this coincidence is relatively frequent.

NEW YORK PATHOLOGICAL SOCIETY

Regular Monthly Meeting, March, 8, 1928

HARRISON MARTLAND, *President, in the Chair*

A CASE OF RECURRENT FIBRO-ADENOMA OF THE BREASTS. MEYER M. STARK.

A fibroma or a fibro-adenoma is not usually considered a malignant tumor, though it can and does recur locally, and not only once, but several times. That a few of these, after several recurrences have shown sarcomatous elements is a matter of not infrequent record. The so-called desmoid of the abdominal

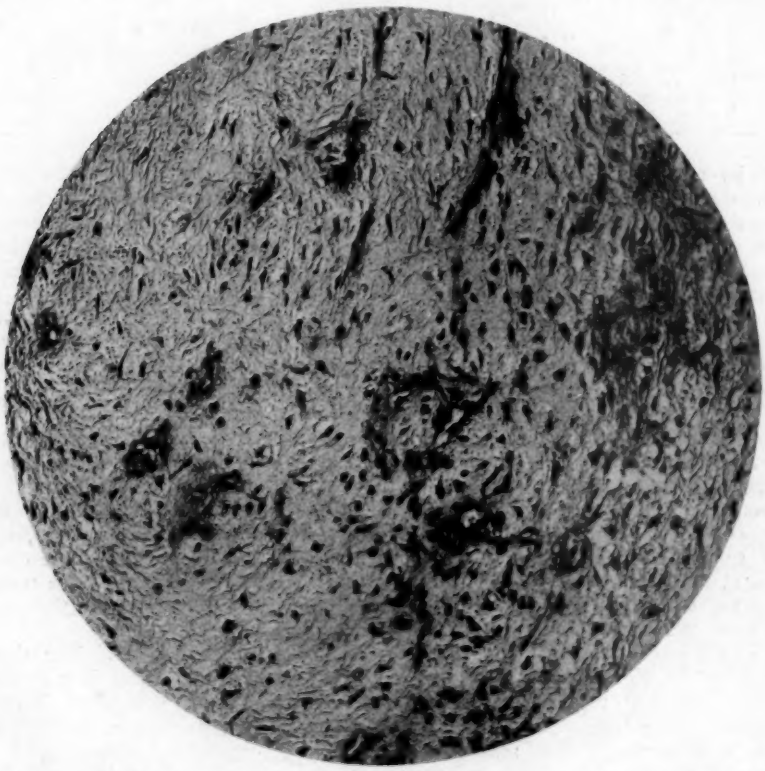


Fig. 1.—Rapidly growing recurrent fibro-adenoma; the second tumor in the right breast.

fascia is a conspicuous example of such a tumor, though I believe that today this type of growth is classed as a sarcoma. When recurrences are frequent, it is a moot question, however, in the case of fibromas, whether such terminal malignancies are true examples of anaplasia, or whether it is not more likely that the original mass contained the very elements which later proliferate and which were not completely removed at the time of the first operation. While my case has not shown any features suggesting malignancy, it is presented as a rare instance of a tumor, recurring in both breasts.

The patient first came to my notice in May, 1920, when she was 44 years old. Two years before, she had noticed a small lump in the right breast, neither painful nor tender, which became accentuated at the menses. It grew slowly.

There was not any loss of weight nor axillary glandular involvement. The tumor was hard, seemed to be freely movable in its bed (or capsule) and was not adherent to the overlying skin; there was not any secretion from the nipple. At operation the tumor, weighing 5 pounds (2.3 Kg.) was easily shelled out from its definite capsule. It was in general hard, but soft and cystic in isolated areas. The pathologic diagnosis was intracanalicular fibro-adenoma. One and one-half years later, in October, 1921, the patient presented a recurrence at the site of the previous operation, the tumor being larger than before. This tumor was also removed. It weighed 7 pounds (3.2 Kg.), and was adherent broadly to the pectoralis fascia; this, with its underlying major muscle, was liberally excised. As before, the axilla was not cleaned out, as

Fig. 2.—Primary tumor, left breast.

there was no glandular condition, and the situation did not seem to call for any more radical procedure than was performed. Again the diagnosis was fibro-adenoma (fig. 1). In view of the recurrence, roentgen-ray treatment was advised and given. It had the desired effect of preventing a return of the tumor, but the treated area has become stony hard and leatherized, and is extensively telangiectatic.

Two years after the second operation (October, 1923), the patient reappeared, this time with a large tumor on the other side, similar clinically to the one encountered on the right side. At this operation, fearing malignancy and recurrence, and in consideration of the actual suffering directly resulting from

the intensive raying, a classic, radical operation was performed, in which was incorporated the added procedure of resection of a part of the rectus abdominis fascia. The axillary glands were not involved; the tumor weighed 9 pounds (4.1 Kg.). Again the diagnosis was fibro-adenoma (fig. 2). Roentgen-ray treatment was not advised, as it was thought that there would not be a recurrence. Nevertheless, three years later (November, 1926), in the very center of the left scar, a recurrence the size of a small orange appeared. It was hard, was easily peeled out and seemed to be lobulated, much as a lipoma would be. Reasonable anxiety prompted the advice that roentgen-ray treatment again be given, but this time it was planned to give such doses, at such

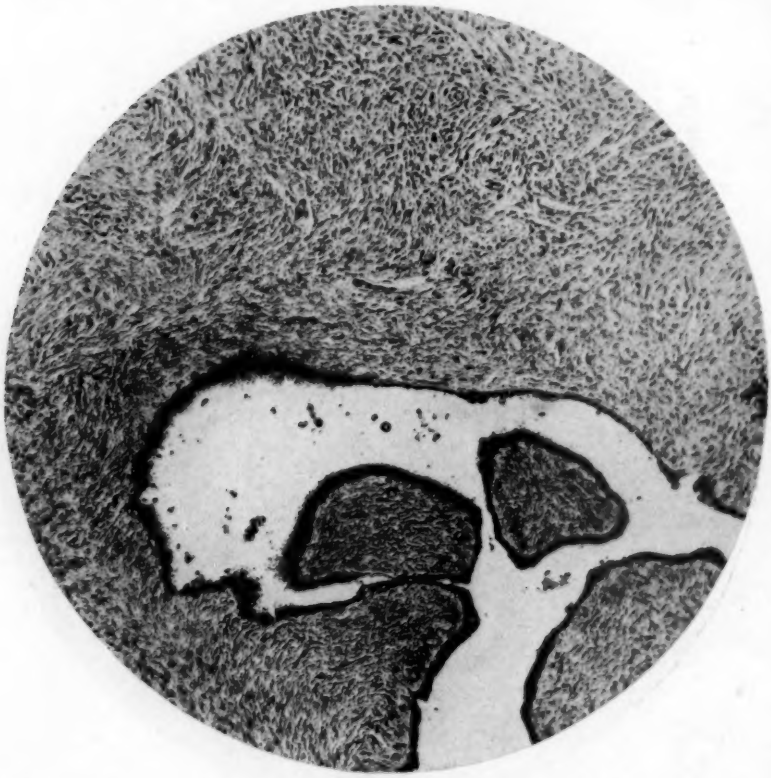


Fig. 3.—Recurrent fibro-adenoma of the breast; the third tumor in the left breast.

intervals, as to tire out any remaining neoplastic cells, without again destroying the viability of the skin (as had occurred on the other side). In spite of a most careful and well planned course of treatment a small nodule appeared one year later (December, 1927), at the site of the former recurrence (on the left side). The nodule was the size of a hazel nut and hard; it was shelled out, and again the same diagnosis was made. The report states that the general appearance of the tumor did not differ from that of the growth removed in 1926, that the type was that of intracanalicular fibro-adenoma, with a cellular stroma, and that there were not any changes which could be attributed to the roentgen-ray (fig. 3).

The practical conclusions from this case are that if the disease can be recognized at the time of operation, the entire breast should be removed. The axilla need not be cleared, as the regional lymphatics are not invaded. Radiation is without benefit either in the treatment of a primary tumor or for the prevention of recurrence. In my case, in the tissue analysis of the growth at the last recurrence, no effects from the roentgen-ray treatment, given for more than one year prior to the recurrence, were revealed.

DISCUSSION

HARRISON MARTLAND: The interesting observation is the occurrence of mitoses in one of the tumors; this, of course, makes the diagnosis of a borderline fibrosarcoma probable.

CHARLES NORRIS: I am much interested in this case. It looks like a case of hyperplastic interstitial mastitis. One is not familiar with this condition because it is rather unusual. The tissues taken from such breasts correspond with the histologic appearance presented. They do sometimes, I believe, become sarcomatous. I see nothing in the photomicrographs which would indicate any malignancy. I have only seen one case clinically, in a healthy woman about the same age as Dr. Stark's patient, who had large breasts. The usual procedure is to remove them, if possible, if the patient is willing.

JAMES EWING: Are not 5, 7 and 9 pounds remarkable sizes for fibro-adenomas? I have never seen anything equal to that bulk. The very size of the tumor should make one a little suspicious about the clinical nature of the disease. Another question is whether in this case there was a real recurrence of the tumor, or the development of a new tumor from other parts of the breast, since in most cases of this type the whole breast is more or less condemned to the growth of tumors, and the tumors are often multiple. I took advantage of the clinical history to express my opinion that the last section is histologically somewhat malignant. I would feel that this might be a more significant comment if Dr. Stark had asked whether or not we thought it was malignant before the history of the case had been given, but it seems to me decidedly more cellular than the ordinary fibroma.

ALFRED PLAUT: The connective tissue in the pictures shown is different from the connective tissue one usually sees in fibro-adenoma. I would like to know whether hyalinization, which is practically missing in any large fibro-adenoma of the breast, occurred in other places. I would like to know about the mass relation between the connective tissue and the glandular elements in these tumors.

Dr. Ewing said that adenofibroma in a breast, on which an operation has been performed for a so-called recurrence, might possibly be explained by the development of a tumor which was too small to be observed at the time of operation.

MEYER M. STARK: Dr. Ewing's second question is answered by what happened on the left side. The entire breast was removed in a most thorough fashion, and yet the tumor recurred; whereas his suspicion about the breast on the right side having a residual tumor might be correct, still I believe the question is answered when he knows that a thorough operation was performed and then a tumor recurred twice in almost the same spot. The subject of malignancy has been thoroughly investigated by a pathologist. It was so thoroughly studied in the last sections especially that I accepted the pathologist's last report that there was no sign of malignancy, and that the mitoses which were questionable in the primary tumor on the left side did not recur; and that is something which has been cited in the literature, that whereas the mitoses might appear in the original tumors they did not reappear in the recurrence. It is a question whether anything remained, and whether, if anything did remain, it underwent sarcomatous change. I cannot answer that, but it appears to me from the clinical course that the tumor is nonmalignant.

The course is parallel with the microscopic evidence. Whether a sarcoma will develop remains to be seen, but if there is any suspicion of a sarcoma, there would be a different type of case history. Metastases will probably be found somewhere after an operation on the breast for sarcoma, as pulmonary metastases are frequent and early.

The work reported from the Crocker Laboratory has a distinct bearing in this situation, namely, the subject of transplanted fibro-adenoma in cats and mice. Those who know of this work know that fibro-adenoma transplanted has the same features, that it can recur many times; and it has been proved that when the recurrences are numerous the terminal ones are of an extremely malignant sarcomatous nature. Again the question arises whether the fibro-adenomatous tissue becomes malignant, or whether malignant tissue not previously removed is brought into the clinical picture. As to other fibro-adenomatous recurrences in breasts, I would say that all are large and few have been reported. Dr. Wood told me that he knows of only four cases in almost 2,000 tumors of the breast. They were all rather large and rapidly growing, suggesting and simulating malignancy from that standpoint, but they were not malignant.

Osteogenic Sarcoma of Scapula Occurring in a Woman Having Previous Radioactive Deposits in Her Body. Harrison S. Martland.

A woman, aged 33, had worked as a painter of dials eight years before I saw her. When applying luminous material to watch dials she was in the habit of pointing the brushes with her lips. She had little trouble with her teeth and never had any extensive necrosis of the jaw.

In September, 1926 (fourteen months before death), she fell, while working in a department store, and hurt her right shoulder. She had pain and limited motion, and was referred to the compensation commission. Roentgenograms showed slight downward displacement of the head of the humerus. She was operated on, but no disease was found in her shoulder. The wound healed promptly without complications.

In July, 1927 (six months before death), she still complained of pain in her shoulder. She also had pain and localized tenderness over the scaphoid bone of her right foot. Examination of the original roentgenograms by Dr. Humphries revealed peculiar changes in the right humerus, scapula and scaphoid bone. From his experience in other cases, he concluded that the condition was osteitis caused by radium; he did not know at the time that the girl had been a painter of watch dials.

In September, 1927 (three months before death), roentgenograms for the first time showed a sarcoma of the right scapula springing from its anterior and upper part, and an osteitis of the right scaphoid bone, with fragmentation.

In December, 1927, she returned to the hospital with her right arm markedly swollen down to the hand, and with pain which was constant and unrelieved by morphine. In order to lessen the pain an operation was performed to relieve pressure on the main trunks. Large masses of tumor tissue were removed. She died a few hours later.

Autopsy showed a large osteogenic sarcoma of the right scapula invading the whole anterior and upper part of the bone with infiltration into the supraspinous and infraspinous muscles. There were no visceral metastases. A profound anemia was present, the yellow marrow in the long bones being entirely replaced by a dark red regenerating marrow. Histologic examination showed the tumor to be an osteogenic sarcoma in which there was considerable cartilage. In places, the growth was cellular, with mitotic figures and hyperchromatism. In other places the growth was sclerotic. New bone formation was common. The bone marrow showed a regenerative anemia of the megaloblastic type. Sections from the scaphoid bone showed the marrow replaced by a loose, gelatinous, myxomatous, fibroblastic tissue in which there was considerable fat.

Dental films, when strapped to the bones, showed positive exposures in from fourteen to 30 days, due to beta and gamma rays, the alpha rays being screened and filtered out by the paper in the dental pack. The bones, when placed directly on photographic films, showed positive exposures in as short a period as three days. After seven days' exposure definite alpha penciling was noted, with the typical irregular distribution and concentration seen and described in earlier cases. Bones dried and partly incinerated showed positive radioactivity when tested with the alpha electroscope. Chemical extraction and determinations of the quantity and character of the radioactive deposits have not been completed. An attempt is also being made to show the presence of radioactive deposits in the sarcoma.

Several features in this case, combined with facts ascertained in a study of the earlier cases, lead us to believe that the pre-existing deposits of radioactive substances in the bones were more or less responsible for the development of the sarcoma.

Peculiar changes in the bone existed long before the appearance of the sarcoma, especially in the scaphoid and head of the humerus. The histologic pictures in the scaphoid are similar to those described by Dr. Ewing as occurring in bones after heavy external radiation. In two other cases lesions have been observed in the scaphoid bones. In several cases extensive crippling has resulted from similar changes in the heads of the femurs and acetabula. In one case similar changes were noted in the dorsal and lumbar spine. I believe that the predilection of these bones for severe osteitis due to radiation is explained by their anatomic position; they are especially liable to pressure and external traumatism.

In the lower and upper jaw which was so frequently the seat of extensive necrosis in most of the early cases, a similar type of osteitis due to radiation existed. Owing to their close proximity to the dirtiest part of the body, viz, the mouth, and to the fact that they have embedded in them the teeth which are often infected, these bones are especially liable to necrosis from superadded bacterial infection. The slightest dental intervention may start an intractable necrosis of the jaw.

In addition, I know of another girl who was treated several years ago for a sarcoma of the lower end of the femur on which it was impossible to perform an operation. She had a profound anemia with necrosis of the jaw. Unfortunately, at this time attention was not paid to the occupational disease, and confirmation, other than the history and roentgenograms, is not available. This patient is included in a series of thirteen patients who are thought to have died from this disease which was contracted in one factory.

If this is true, the incidence alone of two osteogenic sarcomas occurring in a series of thirteen cases of occupational poisoning of this nature is a strong argument for the production of a sarcoma of the bone on a basis of pre-existing chronic osteitis.

RADIOACTIVE SUBSTANCES IN A BODY AUTOPSIED FIVE YEARS AFTER DEATH. A. V. ST. GEORGE and A. O. GETTLER (by invitation).

The body was autopsied five years after death for the purpose of obtaining medicolegal evidence in connection with the death of this girl and several others. The patient had been employed in a factory, painting watch dials with luminous paint, which contained radioactive substances. During the process of applying the paint, the girls were in the habit of taking the brush between their teeth for the purpose of pointing it. Subsequently, the patient developed marked anemia and necrosis of the lower jaw bone. She died, and her death certificate was signed syphilis and osteomyelitis of the jaw.

At autopsy, the surfaces of the body were fairly well carbonized and there was a distinct butyric acid odor from the body. With the exception of the bone-marrow, the organs were rather well preserved. Gross or histologic evidence of syphilis was not found anywhere in the body, nor other anatomic

lesions in any of the organs. The lower jaw bone was missing, with the exception of a small fragment.

The bones (jaw, vertebrae, femur, tibia, skull, metacarpals and phalanges), liver, brain, lungs and spleen were tested for radioactive substances. Every portion of tissue and all the bones gave graphic evidences of the presence of radioactive substances. Every portion of tissue and all of the bones tested gave electroscopic evidences of radioactive substances — all three rays (alpha, beta and gamma). The nature of the emanation was due to radium. The detailed estimate of radium content for the bones, liver and lungs was 11.36 micrograms.

DISCUSSION

HARRISON MARTLAND: I am particularly interested in the photographs shown by Drs. St. George and Gettler. They are much stronger than any of those obtained in my cases. On account of the intensity of these pictures and the short time necessary for their production, I rather expected to find a larger amount of radioactive substances in this case. The amounts recovered are small. The first patient I saw was a chemist who died from a rapidly progressing regenerative anemia. The amount of radioactive substances present in the entire skeleton was estimated by the company's physicist to be about 14 micrograms, of which 45 per cent was radium and the remainder from mesothorium. At that time I was not aware of the importance of the case I was working on, and submitted only a few of the lumbar vertebrae to the physicist for examination. In the next case I had a better opportunity. By chemical methods the radioactive substances were extracted and it was estimated that the skeleton contained about 180 micrograms, of which 70 per cent was mesothorium and its decay products. In the third case 150 micrograms was found. In a case described by Dr. Flinn, in which the gamma electroscope was used during life, he estimated that another girl had about 100 micrograms in her body. The amounts recovered by Dr. Gettler compare with those found by the company's physicist in the first case. At any rate it is seen that the lethal amount, if there is such a quantity in these cases, is extremely small.

My contention has always been that if there is enough radioactive substance deposited in the bones to secure photographs in from five days to two weeks, then during life the hemopoietic centers must have been under a constant bombardment, week after week and year after year. As most of the radioactive substances are deposited chiefly in the phagocytic histiocytes of the sinusoids in the bone-marrow, the destructive alpha rays, which comprise over 95 per cent of the total are allowed to exert a constant irradiative effect on the adjacent blood-forming centers. This, of course, may be a matter of less than 1 mm. in distance. Sooner or later, the early stimulative effects must wear off and be followed by a fatal, regenerative, or possibly aplastic, anemia, if the patient lives long enough. I do not believe the amounts recovered are worth comment. There is now evidence that amounts ranging from 14 to 180 micrograms of radioactive substances deposited in the bones is necessary to produce these fatal anemias. Whether this is radium or mesothorium is of interest so far as prognosis is concerned. If the larger part is radium it is worse for the patient, as it takes 1,750 years to reduce it to one half strength. At present, there is not any way to convert it into soluble forms which may be excreted. However, if the mesothorium predominates, the fatal anemia may develop more quickly, since mesothorium is much more irritative biologically than radium. If the patient should live ten or twelve years there is a possibility of recovery, since by this time most of the mesothorium will have decayed.

The extremely valuable part of Dr. Gettler's work is the finding of considerable radioactivity in organs not connected with the reticulo-endothelial system, for instance, the brain. It suggests that the radioactive substances have not been as fixed as I first thought they were, and that there is still a possibility of eliminating some of the radioactivity. It is of the utmost impor-

tance that Drs. St. George and Gettler continue their studies along these lines, since it offers the only hope in the treatment of these patients.

CHARLES NORRIS: I arise with a distinct sense of humility for the reason that I do not think I can add anything to what Drs. St. George and Gettler have said on this important subject. It has so many points of interest and importance. Evidently, not until Dr. Martland began the work and recognized this disease condition was it generally recognized, and the bearing on the whole matter for public health purposes is of immense value to the community. As Drs. St. George and Gettler have indicated, it is a subject of grave doubt as to how many cases there are in the country, and they are not recognized by the ordinary physician or by the dentists for the good reason that the disease is a new one. I think that the society is distinctly to be congratulated that it has a member who has given to the community such an important contribution to medicine as our president has done. I would like to have had Dr. Gettler tell us, for practical purposes, if any radium or any element is found in normal bone. He knows the point, but he did not bring it out, and I think it would be of great value, if radium emanations were present in the bones of normal persons. One of the most pathetic sights I have ever seen is when I visited Dr. Martland's laboratory in Newark on Sunday, and saw the six young women who were affected with this condition. I was especially impressed with one woman who had an involvement of the upper lumbar and lower dorsal vertebrae, which anybody would have called tuberculosis in a superficial diagnosis. That woman's condition undoubtedly would be misunderstood by the vast majority of physicians with whom she is likely to come in contact. I bring up that case to emphasize how much credit Dr. Martland should have for calling the attention of the community to this important matter.

HARRISON MARTLAND: I should like to ask Dr. Ewing if the changes observed in the bones, especially in the scaphoid, are not similar to those he described as due to external radiation resulting in an osteitis due to radiation.

JAMES EWING: That is an interesting idea, in favor of which one can gather at least two definite points in the evidence presented: The appearance of the sarcoma of the humerus is a little unusual in that the whole bony area, the head of the humerus, acromion and body of the scapula all seem to be altered in the first radiogram. The sarcoma eventually developed from only one portion. The other point is the appearance of the bone marrow. In the scaphoid it is indistinguishable from that which obtained in heavy radiation of bones. However, I think it is extremely difficult to evaluate that evidence. In the first place, one must remember that external radiation capable of producing the described type of osteitis due to radiation is a different matter from the pure effect of radium in the bones. It probably produces a different effect, and there is not any body irritation at work in the cases of ordinary osteitis due to radiation as described in the literature. In the second place, I have seen much the same marrow in large areas of bones which are the seat of spontaneous osteogenic sarcoma, having nothing to do with radium. In the third place, some surgeons would find an adequate cause for the sarcoma in the trauma, which I feel, however, is not a satisfactory explanation. Osteitis due to radiation which occurs in the experience of radiotherapeutists does not offer a record of anything approaching the overgrowth shown.

DOUGLAS QUICK: I think that Dr. Martland's presentation is most interesting. All are familiar with the epithelial growths which develop on the basis of chronic irritation in old postradiated skin following either roentgen-ray or radium therapy, particularly roentgen radiation, since there is a great deal more of it. We know that the clinical course of these growths is a little different from that of similar growths histologically, developing in an otherwise apparently normal skin. They are frequently more circumscribed for a considerable period and often tend to be indolent in character. I think that the possibility of this fundamental and underlying contributory cause extending

itself to the deeper tissues, particularly to the skeletal tissues, as suggested in this case of Dr. Martland's, has not been appreciated.

In the development of skin lesions in a zone of chronic irritation due to previous radiation, the source of radiation has been transient. In the case presented this evening, the source of radiation and irritation was much prolonged, in fact, practically constant, so that it was truly a source of chronic irritation. This might well produce, in the bony parts affected, an ideal setting for the development of new growth, with chronic irritation as a contributory factor.

It is true that the radiographs do not present exactly the characteristic picture of the osteogenic tumors, but it is possible that the clinical course of the growth may be somewhat altered by the change in the tumor bearing or tumor producing tissue, in other words, the tumor bed, to begin with. I think the case is interesting from many angles.

A. V. St. George: In regard to the treatment of the living girls whom we have under observation, it was thought, because of the amount of radium that Dr. Gettler found in the various organs, that possibly some of the radium must be in the circulation. Following the lines of the work of Aub, Minot and their co-workers in Boston on lead poisoning, we tried to treat a number of these girls. Nothing definite has come of it yet, and we are not optimistic; at least, I am not. If something could be done for them, it would be wonderful, because they are slowly going to death. Every few weeks or months a new bone or joint becomes involved. They have received injections of arsenic, and all forms of treatment to stimulate the blood, but apparently it does not make much of an impression on the condition. It is a great industrial hazard, and New Jersey recognizes the disease distinctly as an industrial disease, compensable under the compensation laws. I do not know what the state of New York has done about it.

A. O. Gettler: Normal bones of various parts of the body have been tried and do not show any effect on either the photographic plate or the electroscope.

James Ewing: I should like to know if Dr. Gettler recalls the observation of Lazarus Barlow, who claims to have obtained radioactive substances from gallstones, and whether he has any comment to make on that matter?

A. O. Gettler: Yes, I remember that, but I have never proved it, or disproved it. I might add this: that one might find a slightly faster leak by putting a certain substance, especially in concentrated form, in the electroscope. While the normal leak is sixty minutes, 3,600 seconds, there might be some material that would give a leak of 3,500 seconds. That, in reality, means nothing, and is within the range of experimental error.

Echinococcus Cysts of the Kidney. D. S. D. Jessup.

The gross specimen of a large cyst of the right kidney was shown. The patient had been operated on after a preoperative diagnosis of echinococcus cyst of the liver. The diagnosis was based on the fact that for three years a slowly growing tumor had been present on the right side, without any pain or disturbance of general health. There had not been any urinary symptoms. Furthermore, the patient had been living in Armenia and had a dog in her household there. The cyst measured 17 by 15 by 10 cm., and showed a compressed and atrophied kidney along one edge. Microscopic examination of the kidney tissue showed a marked cellular infiltration made up almost entirely of eosinophils. The blood contained but 6 per cent eosinophils, with a leukocyte count of 12,000. (A complete report will be published later.)

Chondrosarcoma of Costosternal Junction. D. S. D. Jessup.

A woman, aged 34, had a slowly growing cystic growth of the sternum and ribs, which had been noticed for two and a half years. The tumor formed

a protrusion of the skin in the precordial region, and on removal showed several ribs running through its center. Posteriorly it was adherent to the pericardium. Within the thick fibrous capsule was a mixture of cartilaginous tissue with spicules of bone and soft, semifluid, gelatinous material. Sections showed a chondroma invading the fibrous tissue and muscle in the capsule. The blood vessels were also invaded by cartilage cells and in some places only by degenerated matrix. The tumor corresponded to the invading malignant type of chondroma termed chondrosarcoma. The areas of calcification and bone formation appeared to be secondary processes.

DISCUSSION

HARRISON MARTLAND: Has this hyaline matrix been described in the blood vessels so abundantly before?

D. S. D. JESSUP: I have never before seen this type of chondroma or chondrosarcoma which has a tendency to invade the blood vessels, but I think Dr. Ewing refers to this invasive type of chondrosarcoma in his book on neoplastic diseases.

JAMES EWING: I think Dr. Jessup's case is thoroughly studied and interesting on account of the extent of the extracapsular invasion by various kinds of imperfect cartilage. I shall take warning from it and observe all my cases a little more carefully. It suggests to me the possibility of clinically malignant qualities, and I wonder if any roentgenograms have been taken of the lungs. I should expect the tumor to be dangerous.

HARRISON MARTLAND: Are not most of the chondrosarcomas now classified as osteogenic sarcoma?

JAMES EWING: They are, and they form a well recognized group which deserves such classification. In regard to the invasion of the blood vessels, in Prudden's time the remarkable tendency of some apparently benign chondromas to invade the blood vessels was well known.

ALFRED PLAUT: Were any cartilage cells which invaded the surrounding tissue seen in the matrix? I do not see how the matrix can invade the blood vessels.

D. S. D. JESSUP: In answer to Dr. Plaut's question, one of the sections distinctly shows cartilage cells invading the fibrous tissue. In the other sections, I was puzzled to know just how this cartilaginous matrix without cells was streaming through. I think the most probable explanation is that the degenerative process in the matrix of the chondroma is most marked at the periphery, where it is invading the lymphatics and the blood vessels, so in that area it may appear practically free from cartilage cells.

THE SPERMATOCYTE REACTION FOR THE DIAGNOSIS OF TUBERCULOUS FLUIDS. J. E. BLAIR and J. J. WIENER (by invitation).

An attempt was made to apply Long's "spermatocyte reaction" (testicular tuberculin reaction) to the diagnosis of body fluids suspected of coming from tuberculous foci. The test consists of the injection of from 0.1 to 0.3 cc. of the suspected fluid into the testes of a tuberculous guinea-pig; autopsy was performed on the animal after from five to seven days and histologic examination of the testes for a characteristic degeneration was made. Although all positive tuberculous fluids gave the typical reaction, the specificity of the test is impaired by the fact that from 20 to 25 per cent of the nontuberculous fluids (particularly fluids from patients with a malignant tumor) gave a reaction which histologically was indistinguishable from that given by a tuberculous fluid. Data obtained show that this is a toxic effect which possibly can be eliminated, without losing the specific value, by a reduction of the amount of fluid injected.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, March 8, 1928

J. HAROLD AUSTIN, M.D., *Presiding*

SPONTANEOUS TUBERCULOSIS OF RABBITS. MALCOLM J. HARKINS and ELI R. SALEEBY.

Two cases were presented. There was absolutely no connection between them. The first case was observed in a group of eleven rabbits supplied by a local dealer during some studies in syphilis, in which all rabbits were injected with an emulsion of rabbit testicles containing *Spirochaeta pallida*. Thirteen days later they were castrated but macroscopic changes were not noted in the testicles. (Tuberculosis was not anticipated).

The rabbits appeared in good health and 153 days later were autopsied. Nothing was observed except in one rabbit which showed somewhat characteristic lesions in the lungs and on the pericardium. The lesions on the pleura and diaphragm were typical and consisted of numerous irregularly shaped and varying sized nodules. They resembled neoplastic growths more than tuberculosis nodules. Microscopic sections were not typical of tuberculosis but acid-fast organisms were found in smears and sections. Cultures proved these organisms to be the *B. tuberculosis*, bovine type. Three transfers were made and the same lesions reproduced in each instance.

The former owner of this animal could not be traced so that it was impossible to determine the source of infection.

The second case was obscured in a pedigreed rabbit, 8 months old, which had been sick for only three days before death, though the owner stated it had gradually lost weight during the last month of its life, otherwise it appeared healthy. On autopsy it was observed that the lesions were confined to the lungs, pericardium and heart muscle. Macroscopically, they were typical of tuberculosis, and microscopically, they showed characteristic changes, also acid-fast bacilli.

Tissue from this rabbit readily infected other animals (rabbits and guinea-pigs).

It is probable that the source of infection of this second animal was milk, in as much as the owner fed daily supposedly pasteurized milk to his rabbits. The milk was obtained from a nearby commercial dairy. Neither the rabbit owner nor any member of his family have active tuberculosis.

A detailed report of these cases will be published soon.

THE INFLUENCE OF SYPHILIS ON THE INCIDENCE OF PNEUMOCOCCUS TYPES IN LOBAR PNEUMONIA. F. D. W. LUKENS.

A series of 250 cases of lobar pneumonia in which the organism has been typed, have been studied in an effort to ascertain what measurable physical defects in the patient influence the usual incidence statistics of pneumococcus types in lobar pneumonia. Of the many different factors influencing the resistance of the patient, syphilis has been selected for study. It was found in this series that type IV lobar pneumonia has a definitely increased occurrence in syphilitic persons. This observation has also been confirmed in a series of ninety fatal cases of lobar pneumonia in all of which a necropsy was performed. Syphilis was proved by autopsy in twenty-three, and of the syphilitic persons, fourteen, or 61 per cent, had type IV pneumonia. In contrast, syphilis occurred in the other types in from 9 to 17 per cent. The conclusion is that syphilis is an index of host susceptibility and plays a part in deciding the type of pneumonia that the patient will have.

PNEUMOCOCCIC TYPES IN MASTOIDITIS AND MENINGITIS. J. T. BAUER.

This report is based on a series of nineteen typed cases of pneumococcus mastoiditis and pneumococcus meningitis in which no evidence of pneumonia existed on admission to the Pennsylvania Hospital. The organisms were isolated from either the infected mastoid cells at operation, specimens of the spinal fluid or the meningeal exudate at necropsy. Because of differences in the portals of entry, the series has been divided into two groups; first, those with otitis media and secondly, those without a history of otitis media.

The first group consists of fourteen cases of otitis media and acute pneumococcus mastoiditis, of which four died with an acute pneumococcus meningitis. In this entire group, type I was isolated two times, type III ten times and type IV two times. Type II did not occur once. Thus type III is the predominant type occurring in our series of pneumococcus mastoiditis and meningitis following otitis media.

The second group consists of five cases of pneumococcus meningitis in which otitis media was not present. In two of these, the organisms gained access to the meninges by way of the paranasal sinuses which were injured through cranial fractures. In the remaining cases, the portal of entry was not determined. In the second group, type I occurred once and type IV four times. Types II and III were found in none of the cases. Thus type IV is most frequent in our series of primary pneumococcus meningitis in which otitis media was not present.

ADENOMA OF THE ISLANDS OF LANGERHANS WITH HYPOGLYCEMIA. W. U. MCCLENAHAN.

A colored man, aged 42, was admitted to the Pennsylvania Hospital with the history of periodic attacks of loss of memory which had a gradual onset and usually lasted one and a half hours. They generally occurred at midday and were relieved by taking food. Between attacks he was free from symptoms.

The physical examination was essentially negative on admission. On the following day the patient fell into coma from which he never recovered. His blood sugar showed 40 mg. of sugar per hundred cubic centimeters on this day. He developed a terminal bronchopneumonia and died seventy-two hours after admission. The results of the examination of the spinal fluid were negative except for a low sugar content (20 mg. per hundred cubic centimeters of fluid). In spite of the administration of dextrose by gavage, enteroclysis and intravenously, the hypoglycemia persisted and the sugar determinations were 40, 45 and 36 mg. per hundred cubic centimeters on the three successive days.

At autopsy, an encapsulated, vascular nodule was found in the pancreas composed of cells similar in structure and arrangement to those of the islands of Langerhans and associated with a generalized hyperplasia of the islands throughout the pancreas. The suprarenals and pituitary glands were normal. There was no evidence of metastasis, and the eosin and hematoxylin stains of the liver failed to show a significant decrease in its glycogen content.

Numerous cases of hypoglycemia have been observed clinically and twenty cases of adenomas of the islands of Langerhans are recorded in the literature, but the association of these two conditions does not seem to have been observed.

Recently Wilder has, however, reported a case of carcinoma of the islands of the pancreas (*J. A. M. A.* **89**:348 [July 30] 1927) in which hypoglycemia was caused by a malignant tumor of the islands with metastases to lymph glands and liver.

The finding of a lesion of the pancreatic islands in our case associated with hypoglycemia and a significant history would seem to add further evidence toward the recognition of a new disease entity which clinical observations and Wilder's case have already warranted.

EPINEPHRINE GLYCOGENOLYSIS AS A TEST FOR LIVER FUNCTION. SELLING BRILL and THOMAS FITZ-HUGH, JR.

The liver function tests now available in clinical practice are by no means satisfactory. Following a "lead" in the brilliant work of Mann, and in line with other known facts of liver physiology, we were lead to believe that a study of blood sugar curves following injections of epinephrine might give us a method of clinical value for testing one of the liver functions.

Our initial optimism has given place, as our experiments proceeded, to a feeling that this particular liver function test of ours would doubtless fall short clinically in much the same way that other liver function tests have done, because of the old difficulty inherent in all functional testing of an organ with manifold functions and a tremendous margin of reserve. Nevertheless, the sound physiologic bases of the test to be discussed and certain of our experimental results to date justify our belief that it may offer something of scientific if not of clinical value.

The physiologic and pharmacologic bases for the test may be summarized as follows:

1. The well established fact that epinephrine injected in adequate dosage into the animal organism produces a marked rise in blood sugar with a fairly characteristic curve depending on the dosage and method of injection.

2. This hyperglycemia induced by the injection of epinephrine is apparently due to accelerated and augmented glycogenolysis in the liver.

3. The other nonhepatic glycogen stores of the organism such as skeletal and heart muscles, are not acted on by epinephrine in the absence of the liver, and apparently do not play any demonstrable part in glycogenolysis induced by epinephrine.

4. In rabbits whose livers are rendered temporarily glycogen-free, there is no hyperglycemia following injections of epinephrine, whereas when the livers are rendered only partially glycogen-free there is a less marked hyperglycemia of delayed onset.

5. Correlated with these major facts may be mentioned (*a*) the clinical use of epinephrine to combat an overdosage of insulin; (*b*) the lowered sugar-tolerance of animals with experimental liver damage; (*c*) the complete and rapidly fatal hypoglycemia of hepatectomized dogs whose lives can be prolonged by the administration of dextrose but whose status is totally uninfluenced by epinephrine; (*d*) the markedly subnormal glycogen content of the livers of animals with experimental obstruction of the common duct, and finally (*e*) the sometimes successful clinical practice of giving dextrose intravenously to patients with marked damage to the liver.

We planned our experiments along the standard lines of the dextrose tolerance test — substituting, however, an injection of epinephrine in place of feeding or injecting dextrose. The usual fasting blood sugar specimen was taken, then epinephrine injected and other blood specimens removed at fifteen minute intervals for an hour and a half to two hours thereafter. Blood sugar estimations were made promptly and carefully — in most instances by the method of Hagedorn, in a few by the method of Folin and Wu.

Our first work was with patients in the ward at the University Hospital — whom we divided roughly into four clinical groups: (1) normal patients, without evidence of liver or bile tract disease and without any obvious disturbance of carbohydrate metabolism; (2) borderline cases, with no demonstrable liver disease, but with conditions which might presumably influence the liver adversely (e. g., alcoholism without clinical cirrhosis, gallbladder disease without jaundice etc.); (3) cases with mild or relatively early hepatic disease (e. g., mild cirrhoses, early catarrhal jaundice, subsiding postarsphenamine jaundice etc.) and, (4) cases with severe hepatic disease of widespread character (e. g., diffuse carcinoma of the liver, marked atrophic cirrhosis, chronic obstructive jaundice with obvious cirrhosis). To date we have studied twenty-

four cases and have made twenty-eight blood sugar curves in these cases. Eight cases are in the clinically normal group, six in the borderline group, five in the mild hepatic group, and five in the severe hepatic group. In the latter group of five cases we have seen the liver subsequently at autopsy or operation in all instances — and have pathologic slides in three of these.

Our next study was with dogs — first, normal dogs, and second, dogs with experimental obstructive jaundice.

From the results it was obvious that we had hardly yet found the optimum dose of epinephrine. Dogs evidently tolerate much larger doses than human beings. In dogs, while 5 minims of 1:1,000 epinephrine intravenously seems almost adequate, it requires a cubic centimeter or more subcutaneously to produce the typical rise in blood sugar. Hence, our results are of no value whatsoever because all (except one dog which responded typically with 2 cc.) were given entirely inadequate dosage. Similarly, we feel that 5 minim dosage subcutaneously in human beings is inadequate although a fair percentage of normal, borderline and moderate hepatic cases responded to this dosage as we would anticipate. The fact that a few normal human beings failed to respond with hyperglycemia indicates that this dosage is too small for routine use. Intravenous injection of 5 minims in a human subject produced such unpleasant symptoms that this route was abandoned forthwith. We must admit therefore that our pathologic curves are open to criticism on the score of inadequate dosage, and until we have studied many more cases with larger doses we literally do not know whether we have anything or not. However, we feel that some of the results are significant. The total average rise of blood sugar in our normal group was over 36 per cent of the fasting level — whereas the total average rise in our severe hepatic group was 11.5 per cent only, and whenever there was any rise at all in the blood sugar level following epinephrine in these severe hepatic cases it was distinctly a delayed rise with a type curve different from the normal.

Summary: We have presented preliminary experiments designed to formulate a test for liver function based on glycogenolysis induced by epinephrine. Our results are as yet inconclusive. We do not believe that any one functional test can ever be valid for liver disease in general. Nor do we believe that this test will be of much clinical value unless perchance it be found on further work that glycogenolysis is one function of the liver which becomes unreservedly impaired in certain forms of liver disease before other evidences of hepatic breakdown are so obvious that a test is superfluous.

Book Reviews

EPIDEMIC INFLUENZA. A SURVEY. By EDWIN O. JORDAN, Ph.D., Sc.D., Professor of Hygiene and Bacteriology, University of Chicago. Price, $5.00. Pp. 599, with 98 illustrations. Chicago: American Medical Association, 1927.

It is true of many diseases that their severe epidemics have contributed surprisingly to the understanding of their epidemiology; but only of influenza may it be said that opportunities for definitive studies of its clinical as well as its epidemiologic characteristics are limited almost exclusively to its rare and brief intervals of pandemic prevalence, since it is only at such times that this disease is clearly recognizable as an entity. Therefore, a critical review of the literature of the latest pandemic is a work of real necessity, for it is probable that the advance in knowledge achieved by the study of this outbreak will mark the line from which study and attempted control of the next pandemic must start.

At the request of the Committee on Scientific Research of the American Medical Association, the compilation of such a review was undertaken ten years ago by Dr. Jordan, who now presents the results of his long labors in a monograph which not only reviews fully the massive literature of the subject but embodies much material that is essentially new and brings the whole together into a broad discussion of the baffling epidemiology of influenza. It is a difficult task that he has performed. The literature of the recent pandemic, formidable in the first instance because of its enormous mass, presents to the reviewer still greater difficulties by reason of its wide scope, extending into the fields of clinical medicine, pathology, bacteriology and demography, because of many apparent conflicts of testimony, and finally because of its fragmentary character. The last is indeed the greatest difficulty, for notwithstanding its huge volume, the record of the pandemic is deplorably incomplete in all its phases.

The review of the literature of the pandemic presented in this work is by far the most exhaustive that has appeared. The author states that he has omitted many articles which were deemed unessential; but the bibliography, which lists only articles actually cited in the text, comprises more than 2,000 references, and will not be subject to criticism for its omissions. While the literature that is assembled refers principally to the epidemic of 1918-1919, it includes all the more important reports of the pandemic of 1890-1892, with scanty but doubtless proportionate representation for the literature of the interpandemic years, and is extended through 1926. The excellent arrangement and clear type of the assembled bibliography and the careful cross indexes, by author and by subject, contribute much to the value of the book for reference.

The first three chapters of the text, on "General Character of the Epidemic," "Attack Rate" and "Mortality Statistics," give a historical account of the pandemic, tracing the development, in different countries, of its three major waves, and describing their varied characteristics. The picture which is presented is necessarily a complex one, for no definite time or place can be identified as the starting point of the pandemic, and even in its full development the course which it followed in its progress around the world was extremely irregular. Also, for vast areas only incomplete and dubious records are available. The author has, however, made admirable use of the materials at hand. The fragmentary records of mortality and the far scantier actual records of morbidity which have been assiduously collected are carefully and skilfully assembled, and are supplemented by estimates that are shrewdly made. The final summary of mortality due to the epidemic reaches the appalling figure of more than 21,000,000; but, notwithstanding the fact that most of the components which enter into this sum are necessarily based on rather scanty data, one feels confident that the total is conservatively estimated.

The remainder of the book is devoted to chapters on the "Nature and Course of an Attack," "Pulmonary Tuberculosis and Influenza," "Epidemic Encephalitis and

Influenza," "Pathologic Anatomy," "Bacteriology," "Mode of Transmission," "Preventive Measures," and a final chapter entitled "Analysis and Interpretation of the Epidemiological Data."

Of these chapters, the one on "Bacteriology" is of conspicuous merit. In it the voluminous and bewildering literature of this subject is summarized in a review which is admirably arranged and proportioned. The conflicting observations which have been reported on the Pfeiffer bacillus, on filter-passers and on other organisms which have come under suspicion as the specific cause of influenza are presented succinctly, but in sufficient detail to bring out their significance; and though the author carefully points out technical considerations which may influence the interpretation of results, he maintains an attitude of obvious impartiality which adds much to the weight of the review.

The clinical picture of influenza drawn from the literature of this pandemic appears to be essentially identical with that established by the study of previous epidemics, or to differ only quantitatively. A definite addition is made, however, in the ample confirmation of leukopenia as a characteristic feature; and something is added to the clearer portrayal of so-called "typical" cases and of the more severe variants. What is lacking—a deficiency in the literature rather than in the review—is an equally satisfactory account of the frequency and character of the cases of less than average severity, this being the class of cases which is of special epidemiologic importance as possibly forming the link between pandemic influenza and the intercurrent epidemics of less distinctive character.

The recurrent waves of 1918, 1919 and 1920 offered exceptional opportunities for investigating the immunity conferred by an attack of influenza; and in the chapter which deals with clinical features, the results of recent studies of this question are assembled for the first time. A critical analysis of this evidence leads to the conclusion that "an attack of clinical influenza probably confers some measure of protection over a period of a few months, but that after a year or more the presence of immunity in a sizable, previously affected population is difficult, if not impossible to demonstrate." In its bearing on conceptions of the epidemiology of influenza, this is probably the most important conclusion derived from the study of the pandemic.

With respect to the pathologic anatomy of influenzal pneumonia as observed during the pandemic, it seems to be generally agreed that it differed strikingly from that of the pneumonias seen at other times in two respects. These are; first, a remarkable lack of uniformity in the picture presented by cases from different localities and even by individual cases from the same place; second, the occurrence, in many cases, of lesions which a large number of skilled observers consider definitely distinctive. The diversity is attributed usually to differences in character of secondary bacterial infections, and in the stage at which death occurred. As regards the more distinctive lesions, the question which they raise is whether or not they justify the inference that the virus primarily responsible for this pandemic differed specifically and qualitatively from that concerned in more isolated epidemics, such as that of 1915-1916 in the United States. On this point the views of various writers are quoted, but a general conclusion is not drawn.

In his interpretation of the epidemiology of influenza, Dr. Jordan starts with the premise that the disease as observed in 1918-1919 was a specific infection, and begins his first chapter with the statement of two question, namely: "(1) Is it the same disease that was prevalent under the same name in 1889-1890, 1847 and earlier; and (2) may it be identified with any disease occurring endemically or epidemically in the interpandemic years?"

Discussion of these questions occupies a large part of the first and final chapters, and necessarily runs more or less throughout the whole book. In it are given detailed analyses of the epidemiologic features of the dominant pandemic outbreaks of 1890 and 1918, their immediate recurrences, the more remote and less extensive epidemics of interpandemic years, and the influenza-like diseases that recur perennially. The material which is brought together includes much that is original and is analyzed keenly and skilfully. The basic conception which is developed is that the virus of influenza, comprising perhaps numerous strains, is sub-

ject to extensive variations; that pandemics are due essentially to the occasional development of unusual potency in some strain which for a time breeds true; and that decline of the epidemic is due to loss of this potency, influenced, perhaps, by widespread if temporary and partial immunization against the dominant strain. As to the relation which this pandemic virus bears to that which is responsible for interpandemic epidemics, such as those of 1899-1901, 1907-1908, and 1915-1916, the views expressed are ambiguous. However, in the absence of definitive evidence, the author has perhaps done well to refrain from a more positive statement.

Taken as a whole, Dr. Jordan's monograph is a notable contribution to the epidemiology of influenza. It is, moreover, a work so necessary to all students of the subject and one that involves such a prodigious amount of wearisome labor that its compilation may be considered a public service. Of wide interest today as the most comprehensive record of the extraordinary epidemic of 1918-1919, it will probably find its most appreciative readers whenever the next pandemic turns the attention of the world again to influenza.

MOSQUITO SURVEYS. A HANDBOOK FOR ANTI-MALARIAL AND ANTI-MOSQUITO FIELD WORKERS. By MALCOLM E. MACGREGOR. Price, $5.50. Pp. 282. New York: William Wood & Company, 1928.

The present volume was written primarily to provide information concerning the mosquitoes of Mauritius and Rodriguez for members of the medical and health departments of those islands. It is divided into three sections. Part 1 is chiefly concerned with an accurate and interesting account of the general life history and anatomy of the egg, larvae, pupa and the adult mosquito. Part 2 is devoted to the classification, identification, morphology and bionomics of the four species of anopheline and the sixteen species of culcine mosquitoes known to occur in Mauritius and Rodriguez. Although none of the anophelines and only three of the culcines of this group occur in North America, the account will serve as an admirable introduction to the study of the American species. Part 3 gives a detailed account of the technic of the laboratory and the field including such practical topics as mounting methods, dissection and anatomic technic, breeding and rearing mosquitoes, keeping mosquitoes in captivity and collecting larvae and pupae. A brief outline of carrying out antimalaria and antimosquito surveys is given. In agreement with all modern workers on control of malaria, the author stresses the concentration of control measures on the dangerous carriers. The only method, however, which he gives for the determination of these is that of ascertaining what species can be experimentally infected in the laboratory and correlates these results with the observed habits of the mosquitoes. He does not mention the direct method of examining captured anophelines for naturally acquired infections nor the valuable indirect method of using the precipitin test to identify the mosquitoes' blood meal and hence their habits.

The entire work is admirably conceived and illustrated throughout and bespeaks the practical experience and intimate knowledge of the author on the subject. Besides the group of workers for whom the book was primarily written, it will undoubtedly furnish a valuable handbook for all field workers dealing with the mosquitoes as well as an excellent introduction to the study of mosquitoes in general.

SPECIAL CYTOLOGY: THE FORM AND FUNCTIONS OF THE CELL IN HEALTH AND DISEASE. A TEXTBOOK FOR STUDENTS OF BIOLOGY AND MEDICINE. By EDMUND V. COWDRY, of the Rockefeller Institute for Medical Research. 2 volumes. Large Octavo. Cloth. Price, $20.00. Pp. 1376, with 693 illustrations. New York: Paul B. Hoeber, 1928.

Cytology, as stated in the introduction by Alexis Carrel, seeks not only to gain accurate knowledge of the morphology of the cell but also to learn its chemical constitution, the nature of its organs, the functions of its nucleus and cytoplasmic structures and the condition of the cell in relation to its medium. Physiologic and even pathologic aspects are thus not excluded and the interests of the various

sciences and of medicine, often segregated, are here unified. This book on special cytology, regarded as supplementary to an earlier volume on "General Cytology" (University of Chicago Press, 1924), contains in two well-typed and illustrated volumes thirty-seven special articles by authors familiar with their subjects through their own researches. This distinguished authorship affords, besides the stimulus of name, substance with a freshness of observation and thought which sets it apart from ordinary textbooks, and a variety in style and interest not to be achieved by a single compiler. The titles range from the general—the salivary glands, the gastric glands; cartilage and bone, to the more specific—the visual cells and retinal pigment, the specialized systems of the heart, the internal architecture of the nerve cells, neuroglia and microglia: the interstitial tissue of the central nervous system, the cellular changes in the fluid of the mammalian vagina; separate sections are given to the erythrocyte, the lymphocytes, plasma cells, the myeloblast, the granular leukocytes, and to the macrophages or histiocytes. The divisions within the sections reveal the breadth of approach. Under the pineal gland, for instance, are: comparative anatomy, comparative embryology, comparative cytology, physiologic significance, and clinicopathologic evidence. An extensive bibliography appears at the end of each section. This is an extraordinary book and its contents and outlook will bring much satisfaction to the student.

ORGANIC INHERITANCE IN MAN. By F. A. E. CREW, M.D., D.Sc., Ph.D., Director of the Animal Breeding Research Department, The University, Edinburgh. Price, $12.60 net. Pp. 214, including appendix of 60 charts. Edinburgh: Oliver and Boyd, 1927.

The life of William Withering, English physician and botanist (1741-1799), forms a grateful introduction to a work made possible through a lectureship established in his memory at the University of Birmingham. Dr. Crew, the first memorial lecturer, presents in this book the fundamental conceptions of the mechanism of inheritance and relates them with inheritable normal and abnormal characters in man, combining effectively fact, theory, observation and suggestion with nice discrimination and engaging clarity. Lists of the human defects and derangements which have been recorded as heritable, an appendix which illustrates graphically the mode of inheritance of various dominant and recessive abnormal characters, and discussions of resistance and immunity to disease with special references to infectious diseases and tumor growths afford important and interesting information to the general practitioner for whom this book is especially intended. This information also supplies the basis for the sociologic implications of the introductory and concluding chapters in which the physician is exhorted to remain the biologist; not only to repair the "roads along which mankind is being led" but also to "build new roads, if necessary, which shall lead progressively to racial betterment," and to aid in defining social standards that are biologically sound. The bibliography is omitted but desired references will be supplied by the author. The book offers to its readers sound substance delightfully presented.

ASTHMA, ITS DIAGNOSIS AND TREATMENT. By WILLIAM S. THOMAS, M.D. Price, $7.50. Pp. 279, with 20 illustrations in black and white and six in color. New York: Paul B. Hoeber, 1928.

This book gives a good summary of the present state of our knowledge of the nature and cause of asthma as well as of its modern diagnosis and treatment. The explanation of the theories concerning the fundamental nature of asthma successfully avoids the current confusion in terminology by the use of simple language. There is a bibliography of 325 numbers arranged as footnotes. Many readers probably will wish that the references had been made by inserting the names of authors in the text. While the work of the author is satisfactory, the work of the publisher is open to serious criticism. The paper is unnecessarily heavy (the book, octavo, weighs 2 pounds 10 ounces) and there is throughout an undue wasting of space. The spaces between the lines are wider than necessary, and at least three full pages are wasted between each two chapters. Of the 279 pages in the book about 50, that is, practically 18 per cent, are blank.

Books Received

DENTAL INFECTION AND SYSTEMIC DISEASE. By Russell L. Haden, M.A., M.D., Professor of Experimental Medicine, University of Kansas School of Medicine, Kansas City. With a foreword by Dr. Edward C. Rosenow. Price, $2.50 net. Pp. 165, with 63 engravings. Philadelphia: Lea & Febiger, 1928.

SPECIAL CYTOLOGY, THE FORM AND FUNCTIONS OF THE CELL IN HEALTH AND DISEASE. A Textbook for Students of Biology and Medicine by 35 Contributors. Edited by Edmund V. Cowdry, the Rockefeller Institute for Medical Research. Price, $2. Pp. 1,348, with 693 illustrations. Two volumes. New York: Paul B. Hoeber, 1928.

AN INTRODUCTION TO OBJECTIVE PSYCHOPATHOLOGY. By G. V. Hamilton, M.D., Director of Psychobiological Research, Bureau of Social Hygiene, Inc., New York City. With a foreword by Robert M. Yerkes, Ph.D., LL.D., Professor of Psychology, Yale University. Price, $5. Pp. 354. St. Louis: C. V. Mosby Company, 1925.

ASTHMA, ITS DIAGNOSIS AND TREATMENT. By William S. Thomas, M.D., Associate Attending Physician in Immunology, St. Luke's Hospital, New York. Pp. 279, with 20 illustrations in black and white and 6 in color. New York: Paul B. Hoeber, 1928.

DIE MORPHOLOGIE DER MISSBILDUNGEN DES MENSCHEN UND DER TIERE. Von Prof. Dr. Ernst Schwalbe, Herausgegeben von Dr. Georg B. Gruber, o. o. Professor der Patholog. Anatomie an der Universität Innsbruck. III. Teil. Die Einzelmissbildungen XIII. Lieferung 3. Abteilung 4. Kapitel. Die Missbildungen des Darmkanals und der Verdauungsdrüsen, Einschliesslich der Kloakenmissbildungen. Von Privatdozen Dr. H. E. Anders, Freiburg, im Text. Price, 7.50 marks. Pp. 482, mit 60 abbildungen. Jena: Gustav Fischer, 1928.

KONSTITUTIONSSEROLOGIE UND BLUTGRUPPENFORSCHUNG. Von Dr. Ludwig Hirszfeld, Stellvertretender Direktor des Staatlichen Hygiene-Instituts-Warschau. Price, 18 marks. Pp. 235, mit 12 abbildungen. Berlin: Julius Springer, 1928.

THE FORTY-THIRD ANNUAL MEDICAL REPORT OF THE TRUDEAU SANATORIUM AND THE TWENTY-THIRD MEDICAL SUPPLEMENT FOR THE YEAR ENDING SEPTEMBER 30, 1927. Together with the Tenth Collection of the Studies of the Edward L. Trudeau Foundation for Research and Teaching in Tuberculosis. Pp. 460. 1927.

COMMUNICATIONS FROM THE MEDICOLEGAL INSTITUTE OF THE UNIVERSITY OF COPENHAGEN. Vol. VII. 1927.

This is a collection of twenty-two articles published in various medical journals in Danish, French, German and English during 1926 and 1927. The articles constitute important contributions to forensic medicine; many of them have been abstracted in THE ARCHIVES.

FORENSISCHE GYNÄKOLOGIE. Von Prof. Dr. Fritz Reuter. Sonderabdruck aus Biologie und Pathologie des Weibes. Band VIIIy3. Lieferung 40. Berlin and Vienna: Urban & Schwarzenberg, 1928.

INDEX TO VOLUME 5

The star (*) preceding the page number indicates an original article in THE ARCHIVES. No author entries are made except for original articles. Book Reviews, Obituaries and Society Transactions are indexed under these headings, in their alphabetical order under the letters B, O and S, respectively.

PAGE

Abdomen, congenital defect in musculature of wall of 503
Abortion, spontaneous streptococci as cause of 718
Abscess following typhoid mastitis 722
Achlorhydria: See Stomach
Acromegaly, erythrocytosis in 509
Addison's Disease, peculiar degeneration of suprarenals in 708
Adenocarcinoma: See Cancer
Adenoma, of hypophysis, without acromegaly, hypopituitarism or visual disturbances; terminating in sudden death....1083
of intestine 702
of islands of Langerhans, with hypoglycemia 1147
of salivary glands 308
Adrenals: See Suprarenals
Agglutination: See also Bacteria; Blood groups
complement fixation tests and, for Salmonella pullorum infection 532
macroscopic test, rapid method for 529
new type of inhibition phenomenon in 540
Agglutinins, analysis of bacilli of paratyphoid B, hog cholera and paratyphoid A groups 336
immune, in serum and organs of rabbits, distribution of 331
production 746
reaction, Wassermann reaction and, with serum from patients with febrile diseases 532
response to certain Brucella abortus bacterins 333
Albumin, proteins of egg-white and their relationship to blood proteins of domestic fowl, as determined by precipitin reaction 1111
Alcohol, duration of action of 1121
effects in human body *607
poisoning, acute 1120
Alcoholism, acute basal metabolism in 503
Alexander, H. L.: Death from bronchial asthma; report of 3 cases *1003
Alimentary Tract: See Gastro-Intestinal Tract
Alkali excretion of kidney as index of renal function 740
Alkaloids, influence of on bacteria 894
Allergy, allergic irritability in guinea-pigs.1110
bacterial, further studies on; antigen involved in pneumococcus allergy 529
Alopecia, in experimental rat-bite fever in rabbits 329
Ameba, proteus, formation of contractile vacuoles in 523
Amebiasis, bronchopulmonary, amebic bronchitis and peribronchitis 723
Amyloid, hyalin and, origin of 317
of conjunctiva 704
of seminal vesicles 886
origin and disappearance of, in man 883
problem of amylosis 703
Amyotonia Congenita: See Atrophy
Anaphylaxis, anaphylactic behavior in paramecium 724
anaphylactic contraction induced through mucosa of isolated surviving intestine of guinea-pig 332
anaphylactic crisis, pathogenetic and anatomic relations between death from burns and 334
anaphylactic shock in white rats 538
anaphylactic shock, influence of throidectomy on 539

Anaphylaxis—Continued PAGE
anaphylactic shock, peptone shock and curarization 334
anaphylactic shock, reactions of circular muscle of crop during 175
bacterial, rôle of carbohydrate haptens in 1110
effect of histamine on parenteral denaturization of foreign protein 899
erythrocyte, in dogs, effect of dehepatization on 899
idiosyncrasy and, as related to labor 907
influence of heparin on course of, in guinea-pig 175
local hypersensitiveness, general considerations of 330
nonspecific desensitization *1028
passive, cutaneous, in man 899
passive, latent period in, with immune serum of same species 901
skin reaction 499
skin reactions in normal and hypersensitive guinea-pig 899
with egg-white and timothy pollen, in tuberculous guinea-pigs 330
Anaplasmosis, bovine, in Russia 527
Anemia, extramedullary hematopoiesis in ... 144
Gaucher's disease 1083
influence of protein free liver and spleen extracts on blood regeneration and respiratory exchange of anemic rabbits. 688
of rice disease, in pigeons 872
osteosclerotic 315
pernicious, experimental investigation as to possible etiologic relationship of Monilia psilosis to 166
pernicious, morbid process in 921
polyneuritis due to 881
produced by carcinoma in different parts of colon, varying degrees of 182
severe, blood regeneration in 684
sickle-cell 308, 886
toxic, produced by Clostridium welchii ... *429
Anesthesia, ether used for, deaths from impurities in 1119
Aneurysm, cirsoid, of uterus 694
intracranial 553
mycotic, of heart, with destructive lesions of auriculoventricular bundle, without bradycardia; 2 cases 149
of renal artery *223
Angina Pectoris, superior cervical sympathetic ganglion in; microscopic study .. 690
Angioma, lipoma and osteoma of vertebrae .. 884
pathogenesis of 151
Anhydremia: See Blood
Anomalies: See Deformities
Anoxemia: See Blood, oxygen
Anthrax, bacillus 520
bacillus, attempts at infection with single animal 171
bacillus, structure of, and reversal of Gram reaction 520
infection; vaccination and immunity in so-called internal anthrax 895
Antibodies, against fat substances of simple constitution, experimental production of complement fixing 335
anaphylaxis and anti-anaphylaxis, rôle of skin in production of 725
formation by lipoids, nature of protein component in 540
Forssman's antigen and 726
heterophile antigen and 1107
in frog's blood 539
lipoid, formation of, in syphilitic immune rabbits 538
specific, in organism, action of 534
Antigens: See also Antibodies
antigenic action of bacterial lipoids 1116
antigenic complex of Streptococcus hemolyticus 1108, 1110, 1111
antigenic function of bacterial lipoids 1117
antigenic properties of distillates of bacterial cultures 1116

Antigens—Continued PAGE
antigenic properties of glue, wheat and house dust 897
biochemistry of 728
certain constituent cell products of acid-fasts and their antigenic character.... 538
correction for Kahn reaction, principles of 750
for Kahn tests; uniformity in sensitiveness of standard antigen..... 177
heterogenetic, in animal organs..... 729
heterogenetic in organism, and influence of their immunizing function through others of higher specificity..... 539
heterophile, and antibody.....1107
in sensitized dogs; continuous injection of maximum production of precipitin and; quantitative relation between..... 331 730
nonprotein of tubercle bacillus..... 173
precipitin curves following injections of.. 901
rôle of ectoplasms and endoplasms of mouse-typhoid bacilli in immunity reactions 729
serum reaction produced by feeding of...1113
tissue hydration and its relation to susceptibility and immunity; as shown by skin tests in asthma, chronic sinusitis and other infections..... 332
type-specific and species-specific, of type II pneumococcus cells, influence of heating immunization material on antibody-invoking effectiveness of.....1108
valuation of antigenic properties of derivatives of diphtheria toxin by means of ring precipitation method..... 901
Antitoxin, diphtheria, production of..... 176
Aorta, rupture of, following bullet wound.. 548
stream currents in roots of; their action and new model for their demonstration 693
vital staining of..... 512
Aortic Valve, bicuspid..... 921
Aortitis, syphilitic, involvement of aortic valve in 696
Apparatus: See also under Blood Pressure
aid in testing gastric contents for lactic acid *66
investigation of cataphoresis of toxin and antitoxin in Field and Teague and other apparatus 897
modification of electrolytic Gutzeit apparatus for estimation of arsenic in biologic material 738
scopometry, system for optical measurement and study of colloids and other dispersions *49
simplified cataphoresis methods to estimate diphtheria bacillus virulence..... 743
simplified method for cultivation of anaerobes in fluid mediums.....*834
Appendicitis, rudimentary 315
Appendix, motility of..... 141
physiologic relationship between ileocecal valve and 693
Apoplexy: See Brain, hemorrhage
Argyria: See Silver
Arsenic, embryonic pulp and; sarcoma of fowl produced by..... 732
experimental transmission of, to aqueous humor 516
in biologic material, modification of electrolytic Gutzeit apparatus for estimation of 738
influence of iron and, on volume and on other properties of blood.....1082
Arteries, basilar, normal, hidden traumatic tears of 548
carotid, common longitudinal tears of.... 547
carotid, tumors of..... 707
great, obliteration of..... 513
pulmonary, congenital and acquired abnormalities of 1088
renal, aneurysm of.....*223
Arteriosclerosis, of cerebral vessels, relation to hypertension; distribution of arteries supplying pons and medulla.....*365
Arteritis, presenile; cases..... 703
Arthritis deformans, microscopic changes and pathogenesis of..... 158
Ascariasis 138
Ascaris, echinococcus and, skin tests to extracts of 175
in fallopian tube..... 321

PAGE
Ascites, relation of peritoneal mesothelial cells to production of..... 144
Asphyxia, effects of, on blood chemistry.... 323
Asthma, bronchial, death from 3 cases....*1003
bronchial, pathology of..... 509
cutaneous multisensitivity in patients with, and cutaneous reactions with related substances 727
Atelectasis: See Lungs
Atheroma, experimental, production of, with cholesterol 1088
Atrophy, hyalinization and, of cells and tissues 731
yellow, of liver..... 310
Autohemolysin, experimental, in rabbits.... 541
Autolysin, in blood of syphilitic patients... 181
Autopsy, importance of..... 919

Bacillus, abortus, bacteremia in endocarditis 889
abortus, bacterins, agglutinin response to 333
abortus, Bang's disease, rapid macroscopic agglutination method for serum diagnosis of 1113
abortus, epidemic in Phoenix, Ariz., 1922. 519
abortus, infection in man.....723, 1106
abortus, M. Melitensis and; relationship of 719
abortus, thermal death point..... 745
aertrycke and enteritidis in wild rats of San Francisco, incidence of carriers of 522
anaerobe, pleomorphic; etiologic organism in fetal meningitis..... 749
anthracis: see Anthrax, bacillus
bovine piroplasmas 168
clostridium welchii, toxic anemia produced by *429
coli, acid agglutination of..... 180
coli, production of local renal lesions in rabbits by intravenous injections of certain strains of..... 719
coli, reaction of dog to continuous intravenous injections of..... 718
coli, surface tension on growth of Escherichia coli; effect of..... 168
coli, variations in scours type of, from standpoint of bacteriophagic action.... 326
concomitant, separation of invisible virus from 186
Danysz, inheritance of resistance to, in rat 747
differentiation of human and bovine bacilli by complement fixation..... 335
diphtheriae: See Diphtheria, bacillus
does trypanosome of Dourine traverse healthy skin and mucous membrane?.. 169
enteritidis, Gärtner receptor analysis of. 329
enteritidis, Gärtner, type differentiation.. 179
enteritidis, mouse typhoid infection; mode of spread of.....891, 892
fusiformis, biology of..... 719
fusiformis, spirochetes and; sameness between; Heliconema vincenti..... 327
gas, infection of gallbladder..... 723
influenza; dissemination of micro-organisms in form of dust..... 528
influenza, light activated hemolysin produced by 717
Koch, virulence of..... 173
leishmaniasis-dermal, post-kala-azar 168
leprae: See Leprosy, bacillus
paratyphoid B, Bacillus coli and antibiosis between 329
paratyphoid B group, receptor analysis of 336
paratyphoid B group, type differentiation of, with fowl and swine immune serum 329
paratyphoid B; hog cholera and paratyphoid A groups, agglutinin analysis of 336
paratyphoid B, precipitable substances derived from, and from Bacillus typhosus 1109
paratyphoid B, serologic changes in, as influenced by growth with immune serum 336
paratyphoid B, significance of variability for type differentiation of..... 329
paratyphoid enteritidis group, gastrointestinal poison produced by..... 742
paratyphoid enteritidis group, infection of white mice, microbic virulence and host susceptibility in; effect of diet on host resistance 326

Bacillus—Continued PAGE

paratyphoid, infection in guinea-pigs; second type of salmonella naturally appearing in endemic stage 326
paratyphosus B; interconvertibility of R and S bacterial types of, by homologous immune serums 743
pathogenic, of intestine, identification of. 327
pseudotuberculosis (pseudotuberculosis rodentium) from human pathologic foci..1106
salmonella pullorum antigens for complement fixation test, preparation of..... 531
sordellii, cause of malignant edema in man 521
suipestifer and paratyphosus B Schottmüller, relationship between..... 180
timothy, filtrable forms of..... 525
trichinae, influence of glycogen on infection of muscle with..... 349
typhosus: See Typhoid, bacillus
welchii, other hemotoxins and, in vivo, action of 530
welchii toxin in rabbits, duration of immunity to 532
Bacteria, acid-fast, certain constituent cell products of, and their antigenic character 538
adaptation of, rate..... 744
anaerobic, cultivation in fluid mediums; simplified methods for.....*834
cultures, antigenic properties of distillates of 1116
effect of exposure to heated antiserum on subsequent agglutination of.....1109
invisible and filtrable forms of..... 169
linguatula larvae in human liver..... 328
symbiosis, gas production by, with special reference to influence of nitrogenous substances 333
tissue reaction to; effect of organisms nonpathogenic for man in skin of guinea-pigs; effect of certain animal streptococci in skin of rabbits..... 535
transmissible lysis of thermophilic organism 522
visible, filtrable and invisible forms of... 328
Bacteriophage, as filtrable virus..... 756
development of, from killed bacteria..... 896
in sugar mediums, behavior of..... 893
methods of isolating for Bacillus diphtheriae 1101
question of 896
streptococcus 1101
titration of, particulate hypothesis and... 717
Bacterium monocytogenes, infection; monocytes of rabbit in; their staining reactions and histogenesis.....1104
peruvianum, n. sp., secondary invader of lesions of verruga peruana; etiology of oroya fever 1102
Ball, R. P.: Pulmonary atelectasis following thyroidectomy; report of 4 cases with observations at necropsy.....*763
Bartonella, infection, of field mice..... 895
Bell, E. T.: Primary (essential) hypertension; study of 420 cases.....*939
Benzene, relative toxicity of benzol and its higher homologues 906
Benzol: See Benzene
Beriberi, anemia of rice disease in pigeons. 872
Berman, S. L.: Relations between Kupffer cells and liver cells; functional studies *1020
Bile, acids, in serum with liver disease, quantitative estimation of..... 517
calcium carbonate 517
precipitin, lysin and agglutinin tests with 175
toxicity of, influence of liver on..... 140
Bile Ducts, bile expelling mechanism of guinea-pig 1080
common, effect of eliminating sphincter of, on emptying of gallbladder.....1079
extrahepatic, gallbladder and; complete absence of 148
Bilirubin, blood..... 549
Bird pox 335
Birth Injuries, central nervous system and.1121
Bismuth poisoning 341
Black Tongue, in dog, histology of lesions of 353

PAGE

Bladder, diverticulum, pathogenesis of.... 877
experimental stone in..... 307
urinary, bilocular..... 160
urinary, gangrene of..... 752
Blastomyces, pulmonary blastomycosis; its similarity to tuberculosis..... 505
similarity of reticulum in lung in blastomycosis and tuberculosis..... 505
Blepharitis: See Eyelids
Blood: See Erythrocytes; Hemoglobin; Leukocytes; Serum, etc.
anhydremia due to insulin..... 685
bactericidal action of and of serum against staphylococci 336
bilirubin 549
calcium and potassium content of, in total blood, behavior of, in experimentally anemic animals 517
calcium ion concentration during pregnancy and its relation to tetany..... 889
carbon dioxide content of spinal fluid nancy and its relation to tetany..... 889
carotinemia 514
cells, mesenchymal rests and, in adult organism, undifferentiated..... 508
cells, oxygenated and reduced, action of hematoxins on 742
cells, red, of man in normal and pathologic conditions, dextrose content of.. 712
cells, red, sedimentation rate, effect of venous stasis on and on proteins of plasma 312
cells, red, sedimentation test in children. 738
cells, white, histologic demonstration of lipoids in, and their relation to oxydase reaction 509
cells, white, in human, pathologic leukopenic and leukocytic states, rhythmic range of; study of 32 human bone marrows 145
cells, white, normal variations in, under conditions of minimal metabolism..... 876
cerebrospinal fluid and, with special reference to renal diseases and meningitis, xanthoprotein content of; contributions to normal and pathologic physiology of cerebrospinal fluid 692
changes, following operation..... 140
chemistry, arterial, capillary and venous. 517
chemistry, effects of asphyxia on..... 323
chlorides, estimation of..... 911
cholesterol determinations in pulmonary patients 335
cholesterol, effect of radiation on, in malignant disease 731
cholesterol, insulin and hypercholesterinemia 516
cholesterol, lipoid metabolism in rabbits with tar carcinoma..... 906
cholesterol, metabolism, relation of suprarenal gland and spleen to..... 873
cholesterolemia, xanthomatosis and familial cholelithiasis 507
circulation, extrarenal venous, in case of congenital polycystic kidneys; unusual varicocele communicating between splenic and renal veins..... 878
circulation, speed of, periodic variations in 691
coagulability, effect of parathyroid hormone 139
coagulation, researches on anticoagulant substances of 324
composition and respiratory exchanges of, in terminal chronic nephritis..... 500
concentration, in marine fishes.....1096
copper, in human serum..... 164
count, differential, normal guinea-pig; statistical study; Kurloff body.....*616
creatinine 1095
dyshematopoiesis, cancer and.....1119
fibrin, determination in..... 739
fibrin, free bodies of pleural cavity..... 159
foreign bodies, fate of in venous circulation 879
formation, rôle of spleen..... 875
groups, agglutination reaction for determination of 344
groups, among Polynesians..... 745

Blood—Continued PAGE

groups, classification of cancer patients according to, and some investigations concerning isohemagglutination 540
groups, determination of, agglutination reaction for 344
groups, determination of, discernment of human races by, particularly of Russians from Jews 723
groups, determination of, in human blood stains 912
groups, experiences with legal use 737
groups, hemagglutinins of mother and fetus, observations and research on ... 900
groups, identification of spots of human blood 545
groups, in forensic medicine 549
groups in hemophilic family 536
groups, in mental diseases 726
groups, in Northern Argentina 535
groups, in relation to skin transplants ... 901
groups, in tuberculosis 174, 181, 334
groups, interagglutination of human and beef, blood 179
group, is there relation between syphilis disposition and, as well as between blood group and success of syphilis therapy? 537
groups, iso-agglutinability of human blood preserved in different ways 541
groups, iso-agglutinating powers of red blood cells; agent which changes 729
groups, iso-agglutination 341
groups, iso-agglutinins 179, 341, 534
groups, iso-agglutinins, human, observations on irregularities in 331
groups, isohemagglutination, effect of roentgen rays on 541
groups, isoprecipitation, demonstration of 4 groups in humans by 1115
groups, paternity, constitutional peculiarities of, with reference to 546
groups, psoriasis and 179
groups, species reaction 711
groups, testing for, rapid method of 912
groups, theoretical considerations; practical applications 1115
groups, types and predisposition to disease 900
hematinemia 1097
hematopoiesis, extramedullary, in anemias 144
hemopoiesis and epinephrine hydrochloride 513
heredity and biochemical structure of human blood 181
hypercholesterolemia, experimental, and vascular changes 314
hyperproteinemia associated with multiple myelomas 1094
in lymphadenopathies, polymorphonuclear neutrophils in; their relation to classification and radiation treatment *267
in mercuric chloride poisoning, xanthoprotein reaction in 341
leukemic, culture studies of 710
myeloblast, development potentialities of. 161
nonprotein sulphur, concentration of, effect of diet on 684
of allergic persons, transmissible and restraining substances in 180
of new-born children, birth crises in 884
of new-born infants, effect of ultraviolet light on 496
oxygen, acute cardiac dilation produced by anoxemia, significance of pericardium in 872
oxygen, anoxemia; relative importance of nervous, endocrine and vascular regulation in response of cardiac output to. 686
oxygen, effect of anoxemia on size of heart as studied by X-ray 497
oxygen, effects of mild anoxemia on cardiac output of unnarcotized dogs 872
oxygen, unsaturation of venous blood in cardiac failure 925
oxygenated and reduced, action of hemotoxins on 718
phosphates inorganic, and of urine, influence of purine diuretics on 1096
physicochemical and biochemical aspects of malignant neoplasmas 730

Blood—Continued PAGE

picture, white, alterations in, after old tuberculin 178
picture, white, of tuberculous guinea-pig. 328
platelets, thrombocytes in pulmonary tuberculosis 172
platelets, Wright's theory and, origin of .. 882
poikilocytosis, occurrence of, in different diseases 1082
potassium and calcium content of in total blood, behavior of, in experimentally anemic animals 517
pressure, arteriosclerosis and nephritis caused by uranium in rabbit, effect on. *577
pressure, cardiovascular response in experimental nephritis 700
pressure, following suprarenalectomy 684
pressure, high, hypertension, primary (essential); 420 cases *939
pressure, high, primary hypertension and associated hyperthyroidism; 3 cases ... 918
pressure, high, relation of arteriosclerosis of cerebral vessels to hypertension; distribution of arteries supplying pons and medulla *365
pressure, high, systemic, influence on right ventricle and pulmonary circuit 139
pressure, method of repeated intra-arterial systolic determinations in dogs 914
pressure, new indirect method for taking, in animals *630
proteins, of domestic fowl, as determined by precipitin reaction, proteins of egg-white and their relationship to 1111
proteins, of plasma, effect of venous stasis on, and on rate of sedimenation of red blood corpuscles 312
refraction and colloid lability of, in tuberculosis 173
sedimentation rate of erythrocytes in certain tropical diseases 185
sodium content of plasma of mice, relation to susceptibility to inoculable tumor ... 1118
sugar, action of insulin and hypoglycemia on human heart 874
sugar, changes, following injections of peptone in dog 1133
sugar, fluctuation in, during eclampsia, and its relation to convulsions 496
sugar, glycolysis in samples 1122
sugar, hypoglycemia, adenoma of islands of Langerhans with 1147
sugar, in pulmonary tuberculosis 518
sugar, reducing nonsugars and true sugars in human blood 888
threads found in, investigation of 887
transfer of local hypersensitiveness of tuberculous guinea-pigs with blood serum. 330
transfusion, death following 1115
transfusion, harmful sequences 1120
uric acid, influence of fat and carbohydrate diets on level of 324
urine density index 740
vessels, absorption from serous cavities ... 139
vessels, arteriosclerotic vascular rupture and cerebral hemorrhage 1091
vessels, changes, experimental hypercholesterolemia and 314
vessels, in valves of normal hearts; summary from study of hearts from 700 autopsies 356
vessels, metachromatic substance in wall of 314
viscosity of, in pulmonary tuberculosis .. 170
volume and other properties of, influence of arsenic and iron on 1082
xanthoprotein reaction and free and conjugated phenols in blood and spinal fluid of patients with uremia 712
Boltz Reaction: See Cerebrospinal Fluid
Bone, clinical and experimental studies of localized and generalized osteitis fibrosa 152
circulatory factors influencing formal osteogenesis 309
decalcification of, by magnesium citrate ... 551
decalcification, rapid method for *835
estimation of ages from 736
formation, tracheopathia chondro-osteoplastica 156
fragilitas ossium; hereditary aspect; case. 307
growth, chondrodystrophia fetalis 709

Bone—Continued PAGE
growth, long, experimental observations on ... 311
growth, osteogenesis imperfecta in endocrine system ... 511
hardness of ... 316
marrow, human, 32 cases; rhythmic range of white blood cells in human, pathologic leukopenic and leukocytic states ... 145
marrow, reticulum of ... 506
Paget's Disease of, sarcoma complicating ... 142
pathologic histology of leontiasis ossea ... 318

Book Reviews:
Affections of Stomach; B. B. Crohn ... 451
American Type Culture Collection; Catalogue of Cultures ... 190
L'angiene de poitrine et L'angineabdominale; D. Danielopolu ... 759
Asthma, its Diagnosis and Treatment; W. S. Thomas ... 1153
Beitrage zur Kenntnis der mongoloiden Missbildung (Mongolismus) auf grund klinischer, statistischer und anatomischer Untersuchungen; W. M. Van der Scheer ... 937
Clinical Diagnosis by Laboratory Methods: Working Manual of Clinical Pathology; J. C. Todd and A. H. Sanford ... 363
Clinical Pathology; P. N. Panton ... 761
Clinical Pediatrics: Volume 2. New Born: Physiology and Care; C. G. Grulee ... 192
Clinical Pediatrics: Volume 3. New Born: Diseases and Abnormalities; C. G. Grulee and B. E. Bonar ... 192
Comparative Physiology of Internal Secretion; L. T. Hogben ... 450
Diseases of Skin; H. H. Hazen ... 449
Epidemic Influenza: Survey; E. O. Jordan ... 1150
Grundriss der pathologischen Anatomie; G. Herxheimer ... 935
Host-Parasite Relations Between Man and His Intestinal Protozoa; R. Hegner ... 761
Hypotension; A. Friedlander ... 363
Kolloidchemie der Wasserbindung; M. H. Fischer ... 563
Manual of Veterinary Bacteriology; R. A. Kelser ... 191
Der Meskalinrausch, seine Geschichte und Erscheinungsweise; K. Beringer ... 748
Modern Aspects of Diagnosis, Classification and Treatment of Tuberculosis; J. A. Myers; Introduction by D. A. Stewart ... 193
Mosquito Surveys: Handbook for Anti-Malarial and Anti-Mosquito Field Workers; M. E. MacGregor ... 1152
Nerve Tracts of Brain and Cord: Anatomy, Physiology, Applied Neurology; W. Keiller ... 450
Nutrition and Diet in Health and Disease; J. S. McLester ... 452
Organic Inheritance in Man; F. A. E. Crew ... 1153
Physiologie normale et pathologique du globulin; J. Roskam ... 936
Practical Bacteriology, Blood Work and Animal Parasitology; E. R. Stitt ... 562
Praktikum der klinischen, chemischen, mikroskopischen und bakteriologischen Untersuchungsmethoden; M. Klopstock ... 762
Reagenzien und Nährboden; E. Böhm and K. R. Dietrich ... 762
Rise and Fall of Disease in Illinois; I. D. Rawlings, in collaboration with W. A. Evans, G. Koehler and B. K. Richardson ... 934
Segregation and Autogamy in Bacteria; F. H. Stewart ... 562
Special Cytology: Form and Functions of Cell in Health and Disease; E. V. Cowdry ... 1152
Standard Methods of Division of Laboratories and Research of New York State Department of Health; A. B. Wadsworth ... 760
Le syndrome paralytique unilatérale global des nerfs craniens; R. Garcin ... 750
Textbook of Pathology; A. Stengel and H. Fox ... 362

Book Reviews—Continued PAGE
Tired Child; M. Seham and G. Seham ... 749
La vaccination preventive contre la tuberculose par le "BCG"; A. Calmette, with collaboration of C. Guerin, A. Boquet and L. Negre ... 361
Books Received ... 194, 564- 938, 1154
Borax poisoning, fatal ... 907
Borna Disease, experimental study of enzootic encephalomyelitis ... 523
Botulism, clostridium, effect of clostridium sporogenes on toxin production by ... 719
Botulism, serum therapy of, in monkeys ... 1113
Brain, abnormal material in, in rabbits ... 147
anatomic basis of vegetative disturbance in mental diseases ... 158
calcium metabolism and ... 1089
dermoid of fourth ventricle ... 1093
hemochromatosis, iron content of tissues in, with special reference to ... 1088
hemorrhage, apoplectic, changes in Ammon's horn in ... 710
hemorrhage, apoplexy, pathology of ... 319
hemorrhage, arteriosclerotic vascular rupture and ... 1091
hemorrhage, following blow on head; voluntary stripping out of colon; injuries to head and feet in hanging; unusual medicolegal experiences ... 546
hemorrhage, in leukemia ... 1093
hemorrhage, independent terminal, large calcified tuberculoma of cerebrum with ... 1087
lesions, in rheumatic fever ... 557
tumors, metastatic, location ... 561
tumors, with polymorphonuclear leukocytosis of spinal fluid ... 157
wounds; healed needle wound of attempted infanticide ... 547
wounds, reaction of neuroglia and microglia to: cerebral cicatrix ... 1084
Breast, abscess, following typhoid mastitis ... 722
fat necrosis of; 20 cases ... 699
hemolymphangioma of ... 707
osteoclastoma (myeloid sarcoma) of human female ... 312
sarcoma of mammary gland ... 709
Bronchi, primary complex in adult, with focal tuberculin reaction in tracheobronchial lymph nodes; case ... 715
Bronchitis, fibrinous ... 162
Bronchomycoses, simulating pulmonary tuberculosis ... 1098
Bronchopneumonia, calcifying focal ... 314
Bronchospirochetosis, in chickens ... 894
Brucella abortus: See Bacillus abortus
Bullet wounds of entrance ... 735
Burns, anaphylactic crisis and, pathogenic and anatomic relations between death from ... 334

Cadavers, gnawing of by house cats ... 736
syphilitic infection from ... 305
Calcification, deposition of calcium salts in areas of ... 310
of liver; cause of, in general ... *254
Calcium carbonate bile ... 517
content, and potassium content; distribution in normal tissues ... 553
deficiency, and vitamine-D deficiency as factors in lowering resistance to tuberculosis in white rats ... 1099
gout ... 1090
metabolism in brain ... 1089
Calculi, gallbladder, radiologic study of structure of ... 1090
Calves, icterus neonatorum of ... 161
Cancer, anemia produced by, varying degrees of, in different parts of colon ... 182
biologic treatment of ... 733
cells in vitro, characteristic properties of ... 543
cultivation of Glover organism from, ineffectual attempt at ... 541
dyshematopoiesis and ... 1119
effect of increased oxygen tension on ... 339
embryonal, of ovary ... *402
experimental, immunization against metastases in ... 185
hyperplasia and sarcomatosis of lymph nodes ... 542
irradiated, physical chemical changes in ... 183

Cancer—Continued PAGE
linitis plastica with polyposis and adenocarcinoma 750
malignant calcified epithelioma of skin... 709
of breast, so-called colloid.....149, 183
of thymus 733
polyp of lung 187
primary, concealed, of palatine tonsil....1129
primary, double *565
primary, of liver 751
primary, of lung 882
secondary, implanted on endocardium of right ventricle 147
serodiagnosis of by precipitation 542
suprarenal, with pubertas praecox in boy, aged 3 years 687
tar, lipoid metabolism in rabbits with... 906
tar, of seminal vesicles 337
tar, systemic factors in genesis of 542
Capillaries, permeability, micro-injection studies of 496, 1080
Carbohydrate, haptens, rôle of, in bacterial anaphylaxis 1110
Carbon dioxide, formed by action of urease, determination of urea by gasometric measurement of 323
dioxide, in blood and other solutions; a micro method for quantitative determination of; efficiency of paraffin oil as means of keeping carbon dioxide in solution 344
dioxide, preservation of complement in various gaseous environments, with special reference to 747
monoxide, poisoning, acute, in burning building 734
monoxide, poisoning, in private garages; 63 deaths from *43
Cathode Rays, high-voltage, effects of, on skin of rat *195
Celloidin, quick method for preparing tissues *282
Cells, binucleate and giant, in tissue cultures, and similarity of latter to giant cells of tuberculous lesions 312
decidual, ectopic, distribution and significance of 148
dust, endothelial reaction 694
dust, of lungs, and heart failure cells; introduction to problem of immunity... 536
dust, pulmonary, origin of 694
"Golgi Bodies," nature of, in fixed material 326
heart failure, dust cells and; introduction to problem of immunity 536
microchemistry of; chromatin content of normal and malignant cells, as demonstrated by Feulgen's "neucleal reaktion" 1096
peritoneal, mesothelial relation of, to production of ascites 144
structure of connective tissue tumor cells in man 543
sympathicotropic, of ovary and testis.... 505
Cerebellum, arteriosclerosis of cerebral vessels, relation of to hypertension; distribution of arteries supplying pons and medulla *365
cerebral tuberculosis in adults; case reports 875
cerebral tumors, changes in sella turcica in 509
cerebral vein rupture in poisoning with illuminating gas 705
healed tuberculoma of.....1087
Cerebrospinal Fluid, acetic anhydride sulphur in acid test; Boltz test 738
carbon dioxide content of spinal fluid with circulatory disturbances 889
colloidal reaction of takata-Ara in 200 cases 737
containing blood, Wassermann reaction in 551
examination of circulation of, with help of intravenous injections of fluorescein 158
experiments on secretion of 693
in human rabies, finding of 723
Levinson test and glucose content in relative diagnostic value of 1122
micro-estimation of phosphate and calcium in pus, plasma and 550
Cerebrospinal Fluid—Continued PAGE
normal and pathologic physiology of; xanthroprotein content of blood serum and, with special reference to renal diseases and meningitis 692
obtained by suboccipital puncture, interpretation of reactions with 911
organic phosphorus of 712
quantitative estimation of globulin in.... 911
spirochetes in, of syphilitic patients..... 737
tryptophane reaction in 739
Charcot joints, pathology of.....1082
Chemical reaction of physiologic sodium chloride used in Kahn test.....*1050
Chemotherapy, agents of, rôle of reticuloendothelium in cures by 171
interference phenomena in action of chemotherapeutic agents in trypanosome infections 177
of Ehrlich, and certain general principles which should be applied in treatment of all infectious diseases.....1105
Chills, splanchnoperipheral balance during fever and 687
Chloromas, false; abdominal lymphosarcoma with metastasis in craniofacial bones.. 313
Cholera, toxin, preparation and examination of 179
Cholesterol determinations in blood of pulmonary patients 335
in gallbladder, relation between cholesterolemia and deposits of; experimental study 303
metabolism 501
Chondrodystrophia Fetalis; See Bone, growth
Chondroma, voluminous, sacrococcygeal... 902
Chondrosarcoma of costosternal junction...1144
Chordoblastoma; sacrococcygeal; case.....*232
Chordoma, sacrococcygeal.....153, 1083
Chorionepithelioma, ectopic; 2 cases.....1117
Cirrhosis, portal, vascular lesions of..... *23
Clasmatocytes, mobilization and transfer of. *787
Clawson, B. J.: Primary (essential) hypertension; study of 420 cases.....*939
Cloacal malformation 885
Clostridium botulinum, destruction of botulinum toxin by milk bacteria 741
botulinum, effect of Clostridium sporogenes on toxin production by 719
sporogenes, effect on toxin production by clostridium botulinum 719
Coal dust, effect of, on silicotic lung.....1087
Cobra: See Venom
Cold, common 1102
Colobomas, certain abnormal conditions of macular region usually classed as.... 702
Colon, dilatation, familial occurrence of Hirschsprung's Disease 883
voluntary stripping out; injuries to head and feet in hanging; late cerebral hemorrhage following blow on head; unusual medicolegal experiences..... 546
Complement, acton of pancreatic extracts on; relationship between proteoclastic and anticomplementary powers of different enzyme extracts 175
degeneration of, on storage at several temperatures 176
relatively heat stable components of..... 175
rôle of 1116
Complement Fixation Test, differentiation of human and bovine bacilli by..... 335
glycerine preservation of serologic test materials, and influence of heat on glycerinated Wassermann positive serums.1128
in diagnosis of tuberculosis, with special reference to its relation to tuberculin skin reaction; value of..... 334
in tuberculosis, antigen in..... 724
preparation of salmonella pullorum antigens for 531, 532
reaction in glanders..... 728
serum diagnosis of tuberculosis by, according to Besredka, Matify's reaction and sedimentation rate 335
Conjunctiva, amyloid of..... 704
intracellus inclusions of conjunctival epithelium 721
Conjunctivitis, natural, granular, of rabbits 721

PAGE

Copper, in human serum 164
Corpus Luteum, some pathologic forms of. 701
Cranium, broadside bullet wounds 547
intracranial aneurysms 553
suboccipital puncture, interpretation of reactions with cerebrospinal fluid obtained by 911
Crothers, B.: Has pediatrician any place in mental hygiene movement? *677
Cutler, O. I.: Relation of arteriosclerosis of cerebral vessels to hypertension; distribution of arteries supplying pons and medulla *365
Cyanosis, traumatic; pathologic physiology. 307
Cystadenoma of pancreas *261
pancreatitis 514
pseudo-papilliferum malignum of kidney, with metastases in tongue 701
Cystine content of hair and other epidermal tissues 164
Cysts: See under Jejunum; Kidney; Knee; Pancreas; Peritoneum; Seminal Vesicles, etc.
Cytodiagnosis, in affections of large intestine 526

Decalcification, rapid method for *835
Deformity, hereditary, of fingers 147
Degeneration, hyaline, nature of atrophy and hyalinization of cells and tissues 731
importance of, in determining cause of premature death 342
of suprarenals, in Addison's disease 708
Delirium, acute, anatomico-clinical note on 3 cases 703
Dermatitis, pigmented and purpuric, of legs; clinical variety of hemorrhagic syphilis of lower extremities 880
Dermoid, of fourth ventricle of brain 1093
Diabetes Insipidus, diuretic substance 685
elective fatty degeneration of Islands of Langerhans in acute pancreatitis without 320
Diabetes Mellitus, action of insulin on depancreatized dogs when protected by blood serum 686
acute pancreatitis followed by 144
calcium metabolism in 165
experimental, blood lipoids in 500
experiments on operative treatment of ... 501
infectious origin? 167
lipoid storage in 161
"muscle work" and insulin requirement in 1081
primary (essential) hypertension in; 420 cases *939
protracted treatment of, by insulin 691
utilization of dihydroxyacetones by patients 1081
Diaphragm, congenital defect of 160
rupture, of diaphragmatic hernial sac ... 319
waxy degeneration as factor causing death in pneumonia and other conditions 349
Diathermy, experimental study; evidence for penetration of high frequency currents through living body 689
surgical, harmful results from 1121
Dicephaly 317
Diet, deficiency disease in dogs 1080
effect on concentration of nonprotein sulphur of blood 684
fat and carbohydrate, influence of, on level of blood uric acid 324
p_H contents of gastro-intestinal tract in dogs, in relation to rickets and 1095
predisposition and nutrition 140
relation of, to quality of fat produced in animal body 1096
Dihydroxyacetones, utilization of, by diabetic patients 1081
Diphtheria, antitoxic serum of exceptionally high potency, with analysis of its various constituents 897
antitoxin and toxin, determination of by means of precipitation method 727
antitoxin and toxin, physico-chemical nature of 725
antitoxin, production of 176
bacillus, action of, and of related organisms on glucosamine 717

Diphtheria—Continued PAGE

bacillus, bacteriophage for, methods of isolating 1101
bacillus, killed, peroral immunization with 726
bacillus, maltase of 892
bacillus, pathogenic micro-organism resembling; corynebacterium ulcerans 893
bacillus, virulence, simplified cataphoresis method to estimate 743
cultures, intradermal test for virulence of 331
immunization; is Schick test practical? .. 537
immunization, oral; experiments 728
toxin, influence of starch on 1116
toxin, nature of 741
toxin, valuation of antigenic properties of derivatives of, by means of ring precipitation method 901
toxoid-antitoxin floccules 533
Diplococcus, gram-positive, in human protozoal infections 521
green-producing, in measles, specificity of. 520
Disease, passing of, from one generation to another and processes tending to counteract it 891
Diuretics, purine, influence of, on inorganic phosphates of blood and urine 1096
Dominguez, R.: Effect on blood pressure of rabbit of arteriosclerosis and nephritis caused by uranium; influence of other heavy metals *577
Duodenum, aspiration for typhoid bacillus in typhoid fever 722
changes in mucosa in peptic ulcer 322
ulcers, gastric, jejunal and; bacteriology of peritonitis following perforation of .. 525
Dyes, organic, transportation and elimination of, by animal organism 497
Dysentery, bacillus, comparison of 3 different systems of classification: English, German and Japanese 720
Dystopia, crossed, of thymus 318

Ear, tympanum perforations and death from drowning 548, 737
Earthworm, serum treated, smooth muscle reaction in 175
Echinococcosis, biologic methods for diagnosis of hydatid cyst 900
skin tests to extracts of echinococcus and ascaris 175
Echinococcus cyst of kidney 1144
cyst, of orbit in Chinese 875
infection, experimental, in cat and fox ... 890
Eclampsia, relation to convulsions, fluctuation in blood sugar during 496
Edema, annular, of skin, in case of infective endocarditis 498
lymphangiectatic, congenital 496
malignant, in man, Bacillus sordellii, cause of 521
of lungs, after removal of tracheal stenosis 883
Electricity, accidents from 343
accidents, industrial 734
electrocution with a current of 12,000 volts 736
injury to skull from current 342
shock, with alternating current of high voltage, death from; necropsy 545
Electropathology; review of pathologic changes produced by electric currents .. *837
Elephantiasis, congenital 507
Elsberg, C. A.: Ventricular system; its relation to cerebellum: ventriculography and other ventricular evidence in recognition of cerebellar disease *596
Embolism, fat, experimental 1091
fat: 2 fatal cases following orthopedic manipulation 1119
pulmonary, complicating pregnancy, labor and puerperium 906
pulmonary, fatal 311
pulmonary, fatal, postoperative, relation of obesity to 311
septic, following urethral dilatation 907
thrombosis and, of lungs, increasing number of deaths from 883
Embree, H. C.: Alcohol in human body *607
Enamel, human, chemical evidences of organic content of 1097

PAGE

Encephalitis, acute 707
acute, toxic, in children, pathology of postinfectious 352
epidemic, in foxes 749
epidemic, variations in virus of, and of herpes 1105
herpes virus, in guinea-pig 1100
herpetic, experimental, nuclear changes of ganglion cells in 505
perioxialis diffusa, familiar form of 1086
Encephalomyelitis, enzootic (Borna disease); experimental study of 523
Endocarditis, brucella bacteremia in 889
infectious, annular edema of skin in case of 498
subacute streptococcus viridans, hematology of 700
vegetative, due to meningococcus 519
villous 885
Endometrium, changes, caused by silkworm gut used to prevent conception 343
ectopic endometriosis *1054
Endothelioma, dural, of cortex, with unusual complication; case 157
of meninges, multiple and diffuse 157
vascular, associated with thrombosis; peculiar reaction of 887
Endophlebitis, hepatic obliterative 321
Endothelioma, dural, of cortex with unusual complication; case 157
Enzyme, extracts; relationship between proteoclastic and anticomplementary powers of different enzyme extracts; action of pancreatic extracts on complement 175
Eosinophilia, constitutional 707
local, in malignant tumors, significance of 338
Epilepsy, acid-base composition of urine from epileptic child 711
Epinephrine: See Suprarenals, extract
Epithelioma, nasal, of horse 184
producing constituents of tar from rice polishing 185
Epithelium, chronic inflammation and atypical epithelial proliferation 339
Epulis, giant cell, histiogenesis of 158
Erysipelas, standardization of erysipelatis streptococcus antitoxin on man 1112
Erythrocytes, changes in blood following operation 140
effect of dehepatization on erythrocyte anaphylaxis in dogs 899
origin 886
sedimentation rate, in certain tropical diseases 185
sedimentation; relation to fibrin value and cholesterol content and application in tuberculosis *810
structure of 161
Escherichia coli: See Bacillus coli
Esophagus, tuberculous stricture of 875
Exton, W. G.: Scopometry: system for optical measurement and study of colloids and other dispersions *49
Extremities, spontaneous gangrene of 878
upper, free transplantation of, through amniogenic malformation 320
Eyes, amyotrophic syphilitic meningomyelitis: 2 cases with Argyll Robertson pupils 1087
aqueous humor, experimental transmission of arsenic to 516
metastatic sarcoma of iris 316
properties of toxin produced by organism isolated in periodic ophthalmia in horse 743
vacciniform blepharitis due to herpes virus on eyelids 717

Fallopian tube, ascaris in 321
insufflation; 2 cases of death following ... 340
tuberculosis of; genital, in female 155
Fat contents of pathologic thyroids in man; histologic studies *13
lipoids and, in certain endocrine organs. 709
oils and, in lungs; reaction to *380
Feces, cedar oil as aid in finding parasitic ova in 740
Fetus, antenatal infection, factor in fetal morbidity 1097
lithopedion 914

Fetus—Continued PAGE
vaccination, oral, subcutaneous and intravenous, with native fetal organisms 746
Fever, black, post kala-azar dermal leishmaniasis 168
influence of high temperature on guinea-pig tests; histologic changes and effects on reproduction 700
nonspecific Wassermann and agglutinin reactions with serum from patients with febrile diseases 532
Fibro-adenoma, of breasts, recurrent; case. 1136
Fibroma, of intestines 143
ossifying, of jaw 181
Fingers, hereditary deformity of 147
Fluorescein, examination of circulation of cerebrospinal fluid with help of intravenous injections of 158
Fontana-Tribondeau method of modification of spirochete impregnation 552
Ford, F. R.: Electromyographic studies in different types of neuromuscular disturbances *660
Fox, H.: Polymorphonuclear neutrophils in blood in lymphadenopathies; their relation to classification and radiation treatment *267
Fracture, longitudinal, of rib, after coughing 509
Frazier, C. H.: Atypical neuralgia; unsuccessful attempts to relieve patients by operations on cervical sympathetic system *650
Freiheit, J. M.: Effect of pilocarpine and epinephrine in production of specific lesions in stomach of rabbits *411
Fried, B. M.: Primary double cancer *565
Fungus, yeastlike, in normal throats 525
Furunculosis orientalis: See Bacillus leishmaniasis dermal

Gärtner's Bacillus: See Bacillus enteritidis
Gallbladder, calculi, radiologic study of structure of 1090
emptying of, effect of eliminating sphincter of common bile duct on 1079
emptying of, effect of pregnancy on 873
extrahepatic bile ducts and, complete absence of 148
gas bacillus infection of 723
pigment deposits in wall of 704
reduplication of 321
relation between cholesterolemia and deposits of cholesterol in; experimental study 308
true Luschka ducts and Rokitansky-Aschoff sinuses of, in human 143
Gangrene gas, development of, after injections of medicaments 342
gas, following subcutaneous injections ... 910
of extremities, following subcutaneous injuries from blunt force 910
of extremities, spontaneous 878
Gas, illuminating, cerebral vein rupture in poisoning with 705
Gastro-Intestinal Tract, congenital atresia of alimentary tract 147
influence of environmental changes on secretion and intestinal bactericidal function 748
obstruction of upper portion, oxygen content of venous blood of dog after 689
of arthropaths, nephropaths and cardiopaths, histologic observations on 323
p_H contents of, in dogs, in relation to diet and rickets 1095
traumatic rupture of alimentary canal; 2 cases 909
ulcer, acute, traumatic, of small intestines; effects of application of clamps on 879
ulcer, chronic; changes in nerves in wall of stomach in 323
ulcer, experimental, relation of pylorus to duration of 310
Gaucher's Disease: See Anemia
Glanders, complement fixation reaction in .. 728
Gliosis, pathologic anatomy of status dysraphicus 882

PAGE

Globulin, in liquor cerebrospinalis, quantitative estimation of 911
Globus, J. H.: Subacute diffuse encephalomitis; report of case simulating tumor of brain *623
Glomerulonephritis, arteriolar lesions of 309
Glossophytia: See Black Tongue
Glover Organism: See Cancer
Glucosamine, action of B. diphtheria and related organisms on 717
Glycogen, formation, in muscles, relationship of, to pancreas and to epinephrine 1079
influence of, on infection of muscle with trichinae 349
Goiter, adenomatous, simple and cystic, in relation to thyroidectomy, basal metabolism in 1081
amyloid 148
endemic, etiology of 506
experimental, unrelated to iodine 307
fat contents of pathologic thyroids in man; histologic studies *13
metastasis into eye 882
Gold, microchemical demonstration of, in tissues 1124
treatment in experimental tuberculosis of rabbits 172
Goldzieher, M. A.: Hypertrophy of muscle in suprarenal vein in hypertension *1
Golgi Bodies: See Cells
Gonorrhea, purpura of gonococcic origin 894
Gout, calcium 1090
Gram stain: See Staining
Granulocytes: See under Leukocytes
Granuloma, growths in rat caused by B. lapraemurium 168
of tendon sheath 151
Growth of pulmonary orifice 923
relative importance of environmental and intracellular factors in beginning of ... 922
Gynecomastia, associated with testicular changes 161

Hall, G. W.: Torula histolytica meningoencephalitis *689
Halpersohn, M. B.: Rapid method for decalcification *835
Haptenes, heterogenetic 330
Harbitz, F.: Calcification of liver, with remarks on cause of calcification in general *254
Hausman, L.: Forebrain; study and reconstruction based on method outlined by authors *573
Heart, action of insulin and hypoglycemia on 874
aneurysm, with destructive lesions; auriculoventricular bundle without bradycardia; 2 cases of 149
cardiovascular response in experimental nephritis 700
effects of mild anoxemia on cardiac output of unnarcotized dogs 872
effect of pericardium on cardiac distention by X-ray 139
important anastomotic vessel in auricle of human heart 355
lesions, produced by deep X-ray 143
normal, blood vessels in valves of; summary from study of hearts in 700 autopsies 356
oxygen, unsaturation of venous blood in cardiac failure 925
papillary myxoma of right auricle 706
rupture, sepsis and, following industrial accident 736
rupture, traumatic, without hemopericardium 907
sarcosporidial infection of myocardium in man 698
size, effect of anoxemia on, as studied by X-ray 497
tumor of endocardium 317
Hemagglutinins: See Blood, groups
Hematoma, chronic subdural 1082
chronic, subdural, and pachymeningitis hemorrhagica interna; relationship of .. 310
Hematopoiesis: See Blood

PAGE

Hemihypertrophy, 8 cases of 163
Hemochromatosis, iron content of tissues in, with special reference to brain 1088
Hemoglobin, is antigenic action of hemoglobin due to? 533
muscle, in human autopsy material 1094
muscle, of dog, specific precipitin reaction of 1112
Hemoglobinuria, paroxysmal 1115
Hemolysin, action of hemotoxins on oxygenated and reduced blood 718, 742
isohemolysins 745
light activated, produced by B. influenzae 717
normal, heterophil, in animals of guinea-pig and rabbit type 336
streptococcus 533
Hemolysis, antiheterolysin serum in patient with streptococcus endocarditis 1114
preservation of hemolytic serum 1116
Hemophilia and occupational accidents 734
Hemorrhage, into lungs of new-born infants 342
subarachnoid, from medicolegal point of view 544
suprarenal 878
Hemotoxin: See Hemolysin
Heparin, influence of, on course of anaphylaxis in guinea-pig 175
reciprocal action of crop muscle in anaphylactic shock; effect of 175
Hepato-Lenticular Degeneration; clinical, anatomic and experimental study 323
Hermaphrodism, true, in man; report of case with critical review of literature .. 701
Hernandez, X.: Chemical reaction of physiologic sodium chloride used in Kahn test *1050
Hernia, diaphragmatic, hypogastro-etroschisis, spina bifida and left renal agenesia in visible full term child 349
diaphragmatic; rupture of hernial sac ... 319
obturator 1083
strangulated pulmonary; case 509
Herpes, simplex and zoster; investigations on 527
virus, encephalitis in guinea-pig 1100
virus of, and of epidemic encephalitis, variations in 1105
virus, particles, size of 1104
virus, recurring strains of 1100
virus, vacciniform blepharitis due to 717
Hill, H.: Primary round cell sarcoma of pericardium; report of case *626
Hirsch, E. F.: Torula histolytica meningoencephalitis 689
Hirschsprung's Disease: See Colon, dilatation
Histamine, effect of, on parenteral denaturization of foreign protein 899
Hohn method for cultivation of tubercle bacillus 552
Holman, W. L.: Focal infection and elective localization; critical review *68
Hormones, female, sex, in urine of men ... 501
lipoclastic 181
of anterior hypophyseal lobe 308
test of urine, diagnosis of pregnancy by .. 911
Howe, P. R.: Vitamin A deficiency in guinea-pig *239
Hueper, W. C.: Cystadenoma of pancreas .*261
Hyalin and amyloid, origin of 317
Hydatid Cysts: See Echinococcosis
Hydrogen Ion Concentration, intracellular; reaction and permeability of inflammatory and neoplastic tissues 713, 714
relation between loss of acid-fastness of tubercle bacillus and 1099
Hydrogen sulphide, in blood, with uremia .. 518
Hypercholesterolemia: See Blood, cholesterol
Hypernephroma of atypical structure 1087
Hyperplasia and sarcomatosis of lymph nodes 542
Hypoglycemia: See Blood, sugar
Hypophysis: See Pituitary Body

Icterus: See Jaundice
Idiosyncrasy: See Anaphylaxis
Immunity, immunologic specificity of streptococci isolated from various diseases of man 743

Immunity—Continued PAGE
rapid production of, to ricin..... 898
rôle of reticulo-endothelial system in.....1109
Immunization, bovine tubercle bacillus in... 899
influence of heating immunization material on antibody-invoking effectiveness of type-specific and species-specific antigens of type II pneumococcus cells...1108
production of artificial immune serums by method of Mez and Ziegenspeck.....1116
Indol, indicanemia in nephritic patients, and experimental nephritis produced with.. 151
Industry, accidents in, from electricity.... 734
accidents in, hemophilia and..... 734
accidents in; sepsis and rupture of heart following 736
Infantilism, generalized 160
Infection, behavior of granulating wounds of rabbits to various types of..... 166
chancroid, experimental investigations of. 178
cutaneous, penetration of infectious agents into regional lymph nodes and into circulation after 171
early, in rabbits, with bovine tubercle bacillus; relation of monocytes and clasmatocytes to 146
focal, and elective localization; critical review *68
intratracheal, tuberculous, morphology of pulmonary foci in guinea-pigs caused by 328
parasitism and tumor formation.....903, 904
protozoal, gram-positive diplococcus in human 521
streptococcus, in dogs, chronic localized (experimental focal infection)..... 560
Inflammation, process, mechanism of.....1086
Influenza, pathologic anatomy of.....*285, *448
Infrarenal glands, congenital absence of both 705
Insanity, manic and depressive conditions, metabolism in 874
Insulin, absorption of, from alimentary tract of depancreatized dogs when protected by blood serum..... 686
attempt at suicide with..... 344
hypercholesterinemia and 516
hyperinsulinism and hypoglycemia; carcinoma of islands of pancreas..... 144
hypoglycemia and, action of, on human heart 874
in tumor tissue..... 338
influence of local application of, on regenerative activity of skin..... 501
is dextrose a hormone for insulin secretion? 502
Intestine, congenital atresia of..... 884
fibroma of 143
hypertrophy, experimental 354
large, cytodiagnosis in affections of..... 526
large, spontaneous perforation of; fetal peritonitis 187
obstruction, acute 694
obstruction, caused by wandering spleen; case 702
physiologic relationship between the appendix vermiformis and ileocecal valve.... 693
polypi of, with special reference to adenomas 702
small, acute traumatic ulcers of; effects of application of clamps on gastro-intestinal tract 879
small, congenital encapsulation of..... 509
small, influence of environmental changes on gastric secretion and intestinal bactericidal function 748
Iodameba williamsi, and certain mammalian hosts; hostparasite relations between... 715
Iodine, in human and animal organs..... 324
Iron, influence of arsenic and, on volume and on other properties of blood.....1082
metabolism, problem of iron reserve; experimental study 873
Isaacs, M. L.: Nonspecific desensitization.*1028
Islands of Langerhans, elective fatty degeneration of, in acute pancreatitis without diabetes 320
hyaline degeneration of, in nondiabetic persons 695
Isohemagglutination: See Blood, groups

PAGE
Jacobsen, V. C.: Ectopic endometriosis...*1054
Effects of high-voltage cathode rays on skin of rat.....*195
Jaffe, R. H.: Electropathology; review of pathologic changes produced by electric currents *837
Fat contents of pathologic thyroids in man; histologic studies..... *13
Relations between Kupffer cells and liver cells; functional studies.....*1020
Jaundice, calcium, studies in..... 515
hemolytic, recurrence of hemolytic attacks following splenectomy for.....1081
obstructive, experimental, effect on liver. 321
of calves, in new-born..... 161
spirochetal, icterohemorrhagic spirochetosis of chimpanzee transmissible to man 525
Weil's disease and yellow fever..... 890
Weil's disease, leptospira of, comparison of spirochete of yellow fever with.....1103
Jaw, ossifying fibroma of..... 181
Jejunum, primary ulcer of..... 309
ulcers, gastric, duodenal and; bacteriology of peritonitis following perforation of.. 525
Joint effusion, chemical composition of fluid in 1095

Kahn Test, chemical reaction of physiologic sodium chloride used in.....*1050
colloid chemical aspects of..... 750
in experimental syphilis..... 333
reaction, specificity of, in febrile diseases.1122
report of 300,000..... 185
Kala-Azar: See Leishmaniasis
Kast, L.: Toxic anemia produced by Clostridium welchii *429
Kelly, R. G.: Sedimentation rate of erythrocytes; its relation to fibrin value and cholesterol content and its application in tuberculosis *810
Kidney, alkali excretion of, as index of renal function 740
calculi, fibrinous, of renal pelvis..... 510
cellular morphology of, in relation to function 154
cystadenoma pseudopapilliferum malignum of kidney, with metastases in tongue.. 701
echinococcus cysts of.....1144
effect of dietary protein on remaining kidney after unilateral nephrectomy.... 145
fat replacement of, in chronic suppurative pyelitis 917
hypertrophy of, experimental, of rabbits, glomerulus in 505
hypoplasia of 318
in primary (essential) hypertension; 420 cases *939
infarct-like areas in, of tuberculous persons 510
ischemia, temporary physiologic and anatomic changes following; nephritis..... 689
malformation of, rare..... 313
nephroses 145
nephrosis of pregnancy, foreign protein from placenta in..... 517
papilloma of renal pelvis; 2 cases..... 711
polycystic, congenital, extrarenal venous circulation in case of; unusual varicocele communicating between splenic and renal veins 878
roentgen radiation of, effect on.....319, 353
tumors, embryonae of..... 349
Kinney, E. M.: Simple method for staining reticulum *283
Kjeldahl Method, direct nesslerization of digestions 911
Klippel-Feill's Disease: See Neck, abnormalities
Knee, cysts of semilunar cartilages of..... 878
Knowlton, K.: Sedimentation rate of erythrocytes; its relation to fibrin value and cholesterol content and its application in tuberculosis *810
Kolmer-Wassermann Reaction, in pregnancy, reliability of.....1122
Kountz, W. B.: Death from bronchial asthma; report of 3 cases.....*1003

PAGE

Kraus, W. M.: Measurement of cerebral and cerebellar surfaces; technic for making endocranial cast suitable for estimation of internal surface of skull overlying cortex cerebri.....*647
Kussmaul's Disease: See Periarteritis nodosa

Laboratory procedures, movement to standardize 138
Lactic Acid, aid in testing gastric contents for *66
growth stimulating effect of..... 501
Larynx, multiple papillomas of..... 187
Leavitt, F. H.: Cerebellar tumors occurring in identical twins.....*617
Lehmann-Facius-Loeschke technics, experiences with tuberculosis reaction according to 335
Leishmaniasis donavani, in skin and subcutaneous tissue of patients, demonstration of; possible relation to transmission of disease..... 519
oriental sore 890
transmission and cultures in sandflies of leishmania tropica 889
Leontiasis ossea, pathologic histology of.... 318
Leprosy, bacillus, granulomatous growths in rat caused by B. laprae-murium..... 168
Gram stain; resistance of tuberculosis leprosy group of organisms to decolorization with sodium thiosulphate.....*1044
Leptospira, from tap water..... 167
of Weil's disease, comparison of spirochete of yellow fever with.....1103
L'Esperance, E. S.: Embryonal carcinoma of ovary *402
Leukemia, culture studies in leukemic blood. 710
experimental; cases 753
familial 693
granulocytes, question of..... 883
hemorrhages in brain in.....1093
secondary myelosis in tuberculosis..... 708
Leukocytes, changes in blood following operation 140
digestive leukocytosis 881
monocytes and clasmatocytes, relation of, to early infection in rabbits with bovine tubercle bacillus 146
myeloblast, developmental potentialities of 161
myeloblasts, identification of, with vital stains 711
myeloblasts, occurrence under normal and pathologic conditions and relations to lymphocytes and other blood cells..... 710
physiology of digestive leukocytosis..... 886
resistance of, clinical and experimental investigation on..... 887
rhythmic range of white blood cells in human, pathologic leukopenic and leukocytic states; study of 32 human bone marrows 145
with polymorphonuclear leukocytosis of spinal fluid; tumors of brain..... 157
Light, rays, action of, on lymphoid organs.. 151
Lillie, R. D.: Gram stain; quick method for staining gram-positive organisms in tissues *828
Gram stain; resistance of tuberculosis leprosy group of organisms to decolorization with sodium thiosulphate.....*1044
Linguatula rhinaria: See Bacteria
Linton, R. W.: Mobilization and transfer of clasmatocytes *787
Lipase in tissues, particularly tuberculous granulation tissue 1097
Lipoids, antigenic properties in, production of 179
bacterial, antigenic action of.....1116
bacterial, antigenic function of..... 1117
bacterial, immunologic significance..... 535
content, and water content of suprarenals 159
fat and, in certain endocrine organs..... 709
in biology and immunity, significance of. 901
lipid distribution in normal and abnormal liver tissues 888
local and systemic changes induced by lipoid solvents in animals fed on diets varying in vitamin content..... 695

Lipoids—Continued PAGE
storage in diabetes..... 161
Lipoma, angioma and osteoma of vertebrae. 884
retroperitoneal lipomyxosarcoma 930
Lithopedion, demonstration of..... 914
Liver, bilaterality of..... 878
calcification of; cause of, in general.....*254
cancer, primary 751
cirrhosis, experimental 512
cirrhosis; experimental study on genesis of initial stages of..... 312
cirrhosis, in juveniles..... 707
cirrhosis, portal, vascular lesions of..... *23
degenerative changes and functional alternation in parenchyma of..... 314
dehepatization, effect of, on erythrocyte anaphylaxis in dogs..... 899
disease of 686
disease of, esterification of serum cholesterol in 692
disease, quantitative estimation of bile acids in serum with..... 517
effect of experimental obstructive jaundice on 321
effect of peptone on hepatic veins in dog.1132
function, epinephrine glycogenolysis as test for 1148
function, resynthesis of lactic acid with disturbance of..... 692
function tests, results of..... 910
influence of, on toxicity of bile..... 140
iron in, and in spleen of fetuses and newborn babes 1092
Kupffer cells of, reactions of, to injury..1089
Linguatula larvae in, in human..... 328
lipid distribution in normal and abnormal tissues 888
lymphangio-hemangioma of dog..... 560
obliterative hepatic endophlebitis..... 321
phlorhizin necrosis of..... 316
tissue, respiration of..... 141
toxic, damage, new experimental form of, with technical chloranil of chloranil by-product 508
tumor, case of primary mesenchymal hepatoma with necropsy..... 697
yellow atrophy of..... 310
Lowenberg, K.: Rabies in man; microscopic observations *638
Lucia, E. L.: Differential blood count of normal guinea-pig; statistical study, with observations on nature of Kurloff body *616
Lucia, S. P.: Differential blood count of normal guinea-pig; statistical study, with observations on nature of Kurloff body *616
Lucksch, F.: Pathologic anatomy of influenza; review based chiefly on German sources *448
Lungs, abscess, postoperative; experimental study 877
atelectasis, pulmonary, following thyroidectomy; 4 cases with necropsy.....*763
cancer, primary 882
carcinomatous polyp of bronchus of lower lobe of left lung..... 187
cavity, problem of, from pathologic and anatomic point of view..... 721
complete absence of one..... 506
edema, after removal of tracheal stenosis. 883
fusospirochetal disease of.....1098
hemorrhages into, in new-born infants.. 342
in whooping cough, pathologic anatomy of 1092
influence of high systemic blood pressures on right ventricle and pulmonary circuit 139
microscopic examination of, of infants dying at or about the time of birth, forensic importance of..... 545
oils and fats in, reaction to.....*380
parasitic conditions of, simulating tuberculosis 923
silicotic effects of coal dust on.....1087
thrombosis and embolism of, increasing number of deaths from..... 883
traumatic laceration of right lung, without fractured ribs..... 544
tumors, tar-induced, inheritance of susceptibility to 902

PAGE

Lymph absorption from serous cavities.... 139
glands, fibrocaseous, tuberculosis of..... 155
glands, Ranke's stages in tuberculosis and, late caseation of..... 172
Lymph Nodes, hyperplasia and sarcomatosis of 542
puncture of, method for obtaining material by..... 550
regional, penetration of infectious agents into, and into circulation after cutaneous infection 171
significance of hemal nodes.....1086
tracheobronchial, primary complex in adult with focal tuberculin reaction in; case 715
Lymphadenopathy, aleukemic lymphadenosis of pharynx..... 322
polymorphonuclear neutrophils in blood in; relation to classification and radiation treatment *267
Lymphangiohemangioma, of liver of dog.. 560
Lymphangioma, hemolymphangioma of breast 707
Lymphatic System, congenital lymphangiectatic edema 496
distribution of lymphatics defined by fatty acid compounds developed in autolysis of contents 148
registry of..... 492
Lymphatism, status lymphaticus.....*661
status thymicolymphaticus, considered in light of recent work on thymus..... 311
Lymphogranuloma, of stomach, hyaline bodies in..... 318
Lymphoid Organs, action of light rays on.. 151
Lymphosarcoma, abdominal, with metastasis in craniofacial bones; false chloromas. 313
Lysozyme 534

McGregor, L.: New indirect method for taking blood pressure in animals.....*630
McIndoe, A. H.: Vascular lesions of portal cirrhosis.....*23
McNally, W. D.: Alcohol in human body.*607
Sixty-three deaths from carbon monoxide poisoning in private garages.....*43
Magnesium citrate, decalcification of bone by 551
Malaria, congenital..... 527
Malformation, amniogenic, free transplantation of upper extremity through..... 320
Malta Fever, problem for state and municipal laboratories 1104
recent cases of undulant fever in New York State..... 744
with especial reference to Phoenix, Ariz., epidemic of 1922..... 519
Manoilow Reaction, application to determination of paternity..... 724
for determination of sex..... 341
for sexual hormone, alleged significance of 185
Marine, D.: Status lymphaticus.....*661
Mastoiditis, pneumococcus types in.....1147
Measles, etiology of..... 521
specificity of green-producing diplococcus in 520
virus of 722
Medulla, effects on nerve cells of, from experimental exhaustion due to loss of sleep 306
Meinicke's Reaction; macroreaction and microreaction, serodiagnosis of syphilis by 1124
Melanoma, subungual; Hutchinson's melanotic whitlow..... 902
Meleney, F. L.: Fracture into frontal sinuses with discharge of cerebrospinal fluid for over year; report of case with death from pneumococcus meningitis..*694
Meninges, multiple, diffuse endothelioma of. 157
Meningitis, epidemic, fulminant, with death in 9 hours..... 913
experimental, from case of influenzal meningitis 526
experimental pneumococcal, local specific therapy of.....1107
fetal, etiologic organism in; pleomorphic anaerobe 749
pneumococcus types in.....1147

PAGE

Meningococcus, vegetative endocarditis due to 519
Meningomyelitis; amyotrophic syphilitic: report of 2 cases with Argyll Robertson pupils 1087
Menstruation and ovulation in monkeys; possible significance for man..... 499
Mental diseases, blood groups in..... 726
Mercuric chloride, poisoning, xanthoprotein reaction in blood in..... 341
Metabolism, basal, determination of surface area of women and use in expressing.. 549
basal, in acute alcoholism..... 503
basal, in pulmonary tuberculosis....872, 1081
basal, in simple and cystic adenomatous goiter in relation to thyroidectomy....1081
basal, relationship of urinary pigment output to diet and..... 688
calcium, in diabetes..... 165
carbohydrate, of tumors..... 184
effects of synthalin on..... 688
in manic and depressive conditions..... 874
inorganic, alterations in; p_H contents of gastro-intestinal tract in dogs, in relation to diet and rickets.....1095
mineral, in infantile tetany, effect of parathyroid extract on.....1079
minimal, normal variations in white blood cells under conditions of..... 876
of tumors in body..... 337
respiratory quotient of resting muscle... 685
Metacarpus, tumors, central giant cells.... 699
Methyl salicylate poisoning; case..... 906
Meyer, A.: Forebrain; study and reconstruction based on method outlined by authors *573
Micrococcus catarrhalis, sepsis caused by..1106
Micromastix reaction, rapid..... 912
Mitral valve, lipoid deposition in..... 708
Mock, H.: Torula histolytica meningoencephalitis *689
Molluscum contagiosum, cytologic study... 505
Moloney, J. C.: Etiology of migraine.....*684
Monilia from respiratory tract..... 893
psilosis, experimental investigation as to possible etiologic relationship to pernicious anemia of..... 166
Monocytes: See Leukocytes
Monster, dicephalic 1134
Moon, V. H.: Racial variation in size of spleen; comparison.....*1040
Mummies, Egyptian, pathologic anatomy of. 707
Murder, detection of, in dismembered bodies 548
Muscles, circular, crop, reaction of, during anaphylactic shock in pigeons..... 175
hypertrophy, in suprarenal vein in hypertension *1
skeletal, malignant rhabdomyoma of....*775
striated, regeneration of, after enervation 704
tissues, action of oils..... 700
Mycosis, splenic; histologic study..... 149
Myeloblasts: See under Leukocytes
Myelomas, multiple; case.....309, 876
multiple, hyperproteinemia associated with 1094
Myelosis aleukemic: See Leukemia
Myocarditis in trichinosis..... 885
Myomas, of stomach, clinical and statistical observations on..... 313
Myositis ossificans progressiva..... 308
Myxoma, papillary, of right auricle..... 706

Nasopharyngeal washings, anaerobic microorganisms in..... 168
Neck, abnormalities of cervical vertebrae.. 710
Negri Bodies: See Rabies
Neoarsphenamine, immunologic reactions after sterilizing treatment with..... 180
Neoplasm, of chest..... 312
rabbit, inability to transmit by cell-free materials 337
Nephrectomy, unilateral, effect of dietary protein on remaining kidney in adult white rats after..... 145
Nephritis, acute, study of inorganic constituents of serum in children with.... 711
arteriolar lesions of glomerulonephritis.. 699

Nephritis—Continued PAGE
chronic, terminal; composition and respiratory exchanges of human blood in... 500
experimental, and indicanemia in nephritics produced with indol..... 151
experimental, cardiovascular response in. 700
gastric secretion in..... 690
physiologic and anatomic changes following temporary ischemia of kidneys.... 689
tubular (nephrosis), in children, and its relationship to other forms of nephritis 1084
Nervous System, central, injuries at birth and 1121
Nesslerization, direct, of Kjeldahl digestions 911
Neuberg-Klopstock technic, experiences with tuberculosis reaction according to..... 335
Neuritis, multiple; polyneuritis due to anemia 881
Neuroblastoma, malignant..... 308
sympathicum 733
Neurofibromatosis, Recklinghausen's disease with partial intramedullary localization 883
Neurohypophysis: See Pituitary Body
Niemann's Disease, lipoid cell splenohepatomegaly, chemical analysis of spleen... 713
Nipple, Paget's disease of..... 511
Nitrobenzene, changes in oxygen capacity of blood pigment of rabbits following administration of..... 688
poisoning 910
Nose, occurrence of brain tissue in..... 879
stenosis, actual and potential damage resulting from 909
Nutrition, normal and zinc..... 688

OBITUARIES:
Danysz, J.....1076
De Witt, Lydia M.....1076
Von Gruber, Max..... 138
Noguchi, Hideyo.....1077
Stokes, Adrian 138
Wright, James Homer..... 494
Occipital Bone, middle occipital fossa..... 544
Oil, cedar, as aid in finding parasitic ova in feces 740
fats and, in lungs, reaction to.....*380
in muscle tissues, action of..... 700
Oligodendroglia, mucoid degeneration of... 158
Ophthalmia, periodic, in horse, properties of toxin produced by organism isolated in 743
Opie, E. L.: Pathologic anatomy of influenza; based chiefly on American and British Sources.....*285
Optochin: See Pneumococcus
Orbit, echinococcus cyst in Chinese..... 875
Oriental Sore: See Leishmaniasis
Oroya Fever, etiology of; bacterium peruvianum, n.sp., secondary invader of lesions of verruga peruana.....1102
Osteitis fibrosa, localized and generalized; clinical and experimental studies of... 152
Osteochondritis deformans juvenilis, histopathogenesis of; basis of early case.. 320
Osteoclastoma (myeloid sarcoma), of human female breast..... 312
Osteogenesis: See Bones, growth
Osteoma, lipoma and angioma of vertebrae. 884
Osteosclerosis, osteosclerotic anemia..... 315
osteosclerotic anemia secondary to epidermoid carcinoma 504
Ovary, embryonal carcinoma of.....*402
of mouse, changes in, following exposure to X-ray; irradiation at or before birth 506
pathologic forms of corpus luteum..... 701
placental and ovarial hormones..... 690
testis and, sympathicotropic cells of.... 505
Ovulation and menstruation in monkey; possible significance for man..... 499
Oxidase, peroxidase and, modification of peroxidase reaction with sodium nitroprusside and benzidine.....*447
reaction, histologic demonstration of lipoids in white blood cells and their relation to 509
staining, method of..... 552
Oxidation and reduction of immunologic substances 724

PAGE
Oxygen, increased tension, effect of, on carcinoma 339
pressure, in air, some pathologic changes in the tissue during attempted acclimatization to alterations of..... 880

Pachymeningitis, interna, hemorrhagic, chronic subdural hematoma and, relationship of 310
interna, hemmorrhagic, medico-legal significance of..... 546
Paget's Disease: See Bone; Nipple
Pancreas, carcinoma of island of; hyperinsulinism and hypoglycemia..... 144
cystadenoma of *261, 514
cysts 152
cyst, content of..... 713
fatty replacement of..... 510
hypoplasia of..... 159
internal and external secretions of..... 692
internal secretion of, function of, in fat resorption 502
regeneration of 1088
relationship of glycogen formation in muscles to epinephrine and.....1079
rôle of excretory system in pathologic anatomy of 149
thyroid and, alleged interrelationship.... 685
Pancreatitis, acute, without diabetes, elective fatty degeneration of islands of Langerhans in 320
Papilloma, malignant, of stomach..... 751
multiple, of larynx..... 187
of renal pelvis; 2 cases..... 711
Paralysis, infantile, fund for study of, in California 304
Paramecium, anaphylactic behavior in.... 724
Parasites, parasitic conditions of lungs simulating tuberculosis 923
parasitism, infection and tumor formation 903, 904
Parathyroid, extract, effect of, on mineral metabolism in infantile tetany.....1079
hormone, effect on blood coagulability.... 139
hormone, existence of..... 139
Paratyphoid infection in guinea-pigs.....1103
Parenchyma of liver, degenerative changes and functional alteration in..... 314
Paronychia, subungual melanoma; Hutchinson's melanotic whitlow..... 902
Pasteur Institute in Montreal..... 305
Pasteurella avicida, comparison of effectiveness of, by oral, subcutaneous and intravenous methods..... 746
Paternity, constitutional peculiarities of blood with special reference to..... 546
Pathologists wanted by U. S. Government.. 305
Patterson, M. B.: Toxic anemia produced by Clostridium welchii.....*429
Periarteritis nodosa 321
nodosa, myelo-neuromyopathic form of Kussmaul's disease 880
Pericardium, diverticula..... 157
primary round cell sarcoma of; case....*626
significance of, in acute cardiac dilatation produced by anoxemia..... 872
Perineuritis, hemorrhagic capsular..... 705
Periosteum, juvenile hypertrophic periostitis 317
Peritoneum, absorption from serous cavities 139
living, permeability of, for toxins, antibodies and foreign proteins..... 536
multiple cysts of, and their histogenesis.. 754
Peritonitis, bacteriology of, following perforation of gastric, duodenal and jejunal ulcers 525
fetal; spontaneous perforation of large intestine 187
tularemic 520
Peroxydases: See Oxydase and Peroxydase
Perthes' Disease: See Osteochondritis deformans juvenilis
Pertussis: See Whooping Cough
Peterman, M. G.: Microprecipitation test for syphilis *445
Petroff, S. A.: Simplified method for cultivation of anaerobes in fluid mediums..*834
Phagocytes, origin of alveolar phagocyte studies in paraffin sections of tissue stained supravitally with neutral red.. 695

PAGE

Pharynx, aleukemic lymphadenosis of..... 322
Phlebitis, postoperative..... 311
Phlorizin necrosis of liver..... 316
Phosphorus, micro-estimation of phosphate and calcium in pus, plasma and spinal fluid 550
poisoning, acute..... 907
Pilocarpine and epinephrine, effect of, in production of specific lesions in stomach of rabbits.....*411
Pineal Gland, tumors.....1083
Pinkerton, H.: Reaction to oils and fats in lung *380
Pinner, M.: Sedimentation rate of erythrocytes; its relation to fibrin value and cholesterol content and its application in tuberculosis *810
Pituitary Body, adenoma of, without acromegaly, hypopituitarism or visual disturbances, terminating in sudden death 1083
dystopia of neurohypophysis..... 706
hormone of anterior hypophyseal lobe; demonstration of presence..... 308
human, glandular elements in posterior lobe of..... 1084
relation between hypophysis and genital organs 502
titration of bacteriophage and particulate hypothesis 717
Placenta, hormonal sterilization of female animals 692
human, origin of common cystic structures of..... 504
in nephrosis of pregnancy, foreign protein from..... 164
leukocytic infiltration of..... 1090
Pleura, formation of adipose tissue in..... 507
histophysiology of and reactions of pleura of guinea-pig to tar and olive oil..... 881
proteases and antiproteases of pleural exudates 516
Pneumatosis cystoides intestinorum.....514
Pneumococcus, effect of pneumococcus culture broth on phagocytic action of antipneumococcus serum 899
febrile reaction from intravenous injection of protective substance in antipneumococcus serum 1114
infection, experimental, mechanism of recovery from 1109
optochin-fastness of..... 531
precipitin reaction of antipneumococcus serums 1107
rough, in vivo, occurrence of..... 891
separation of phosphorus and some inert protein from water-insoluble precipitate of antipneumococcus serum.....1114
smooth and rough, comparative study of. 891
type II, type-specific and species-specific antigens of, influence of heating immunization material on antibody-invoking effectiveness of.....1108
type IV obtained during epidemic, immunologic relations of..... 532
types in mastoiditis and meningitis.....1147
types, influence of syphilis on incidence of, in lobar pneumonia.....1146
Pneumonia, calcifying focal bronchopneumonia 314
lobar, influence of syphilis on incidence of pneumococcus types in.....1146
rheumatic 558
Pneumonomycosis penicillina, industrial disease 1105
Pneumothorax, free fibrin bodies of pleural cavity 159
Poisoning, carbon monoxide, acute, pathologic anatomy of.....1120
Poliomyelitis, experimental, immunization in 330
milk-borne epidemic of..... 518
signification of age distribution of..... 715
Pollen, extracts, preparation and purification of..... 331
timothy and egg-white, sensitization of tuberculous guinea-pigs with..... 330
Polycythemia, polyglobulia induced by cerebral lesions 500
Polyglobulia: See Polycythemia
Polynesians, blood groups among..... 745

PAGE

Polyneuritis: See Neuritis, multiple
Pons Varolii, hemorrhage..... 707
Potassium and calcium, content of and distribution in normal tissues..... 553
Pott's Disease: See Spine
Precipitin curves following injections of various antigens 901
quantitative relation between antigens and maximum production of..... 730
reaction, diagnosis of rabies by..... 900
reaction, observations with..... 330
specific, of muscle hemoglobin of dog..1112
valuation of antigenic properties of derivatives of diphtheria toxin by means of ring precipitation method..... 901
Pregnancy, diagnosis of, by hormone test of urine..... 911
effect of, on emptying of gallbladder.... 873
hematinemia in.....1097
Kolmer-Wassermann reaction in, reliability of 1122
labor and puerperium, pulmonary embolism complicating 906
nephrosis of, foreign protein from placenta in..... 164, 517
Pringle's Disease: See Sebaceous Glands, tumors
"Procutines," in tuberculin papules; demonstration of 178
Prostate, biochemical study of prostatovesicular secretion 889
Proteases and antiproteases of pleural exudates 516
Protein, bacterial; alcohol-soluble proteins in bacteria..... 720
dietary, effect of, on remaining kidney in adult white rats after unilateral nephrectomy 145
foreign, effect of histamine on parenteral denaturization of..... 899
hyperproteinemia associated with multiple myelomas 1094
hypersensitiveness, transmission of, from mother to offspring..... 898
of egg-white, and their relationship to blood proteins of domestic fowl, as determined by precipitin reaction....1111
undigested, in human being, absorption of; simple direct method of studying.. 331
urinary, not originating in blood.....1094
urinary, origin of.....1094
Protozoa, infections, human, gram-positive diplococcus in 521
Psoriasis, and blood grouping..... 179
Psychoses, anatomic basis of vegetative disturbance in mental disease..... 158
Puerperium, labor and pregnancy, pulmonary embolism complicating..... 906
Pulmonary Valve, stenosis, congenital, of conus arteriosus with ectasia of pulmonary artery and bacterial endocarditis of 920
Purpura, of gonococcic origin..... 894
Pyelitis, chronic suppurative, fat replacement of kidney in..... 917
Pylorus, relation of, to duration of experimental gastric ulcer..... 310
stenosis of, effect of, on gastric secretion 686

Rabies, diagnosis of, by precipitation reaction 900
inoculation in.....1105
Negri-negative 328
spinal fluid findings in, in human..... 723
Radiation, effect of, on blood cholesterol in malignant disease..... 731
influence of, on cholesterol in vitro..... 732
Radioactive deposits in body of woman previous to osteogenic sarcoma of scapula 1140
substances in body autopsied 5 years after death 1141
Ramsey, T. L.: Sacrococcygeal chordoblastoma; report of case.....*232
Rat-Bite Fever, experimental, in rabbits; alopecia in..... 329
Recklinghausen's Disease: See Neurofibromatosis
Recurrent Fever: See Relapsing Fever

PAGE

Relapsing Fever, epidemiology of, rôle of bugs in....526, 895
immunity in; influence of reticulo-endothelial system....537, 538
Reproduction, histologic change and effects on; influence of high temperature on guinea-pig testis.... 700
Respiration, effect of overbreathing and of breathing relatively high concentrations of carbon dioxide on urinary excretion of water and chlorides.... 874
respiratory gases, effects of, on density of blood and other fluids.... 164
under increased air pressure.... 141
Respiratory Quotient: See under Metabolism
Respiratory Tract, monilia from.... 893
Reticulo-Endothelial System, effect of blocking of, on natural and acquired immunity 534
in cures by chemotherapeutic agents.... 171
influence of; immunity in relapsing fever 537, 538
myelopoiesis and, effect of toxins on.... 322
primary tumor of lymph gland originating in; case 902
relations between Kupffer cells and liver cells; functional studies....*1020
rôle of, in immunity....1109
simple method for demonstrating cells of 740
Reticulum, fibrils, origin of.... 694
of bone marrow.... 506
simple method for staining....*283
Rhabdomyoma, malignant, of skeletal muscle *775
Rhamy, B. W.: Quick celloidin method for preparing tissues *282
Rheumatic Fever, lesions of brain in.... 557
lesions of, compared with lesions produced by Streptococcus cardio-arthritidis 556, 559
pathology of; 2 cases presenting unusual cardio-vascular lesions.... 696
rheumatic pneumonitis 558
skin reactions in....1112
Rhinoscleroma, of larynx and pharynx in 2 immigrants 1125
Ribs, prevention of regeneration of; problem in thoracic surgery.... 142
Rice Disease: See Beriberi
Ricnter, C. P.: Electromyographic studies in different types of neuromuscular disturbances *660
Ricin, rapid production of immunity to.... 898
Rickets, experimental, influence of thyroid gland on production and control of... 872
*p*H contents of gastro-intestinal tract in dogs, in relation to diet and....1095
rachitic-like disturbance in extreme hypothyroidism 497
Rigor Mortis, appearance of, as determined by experiments on rabbits.... 708
Ringworm, experimental, infection in horses and immunity in.... 169
Rocky Mountain Spotted Fever, another death among workers on....1076
Roentgen Rays, bactericiual action of; research on 169
biologic effects of; investigation with explanation method 503
deep, heart lesions produced by.... 143
dosage, biologic measure of....1118
effect of pericardium on cardiac distention by 139
effect on isohemagglutination.... 541
effect on kidney....319, 353
effect, on unicellular organisms.... 503
of different wave-length, quantitative biologic effects of.... 879

Sachs-Georgi Reaction: See Syphilis
Sacrococcygeal chordoblastoma; case....*232
Saliva, normal, hydrogen ion determination of 888
test ("Docimasia Sialica") in new-born. 341
Salivary Glands, adenoma of.... 308
Sanocrysin, microhistochemical, gold reactions on tuberculous patients treated with 163
treatment in experimental tuberculosis of rabbits 896
Sarcoma: See also Cancer; Tumors; and under names of sarcomas

Sarcoma—Continued PAGE
after war injuries.... 733
chicken, immunity to.... 340
giant cell, prognosis and treatment of.... 730
inclusion bodies in, in dog.... 903
Jensen's rat; cytologic study of cultures in vitro of 1118
metastatic of iris.... 316
multiple, hemorrhagic, cutaneous, of Kaposi 505
of mammary gland.... 709
of omentum 142
osteogenic, of scapula, occurring in woman having previous radioactive deposits in her body 1140
primary, of lymphatic glands, of reticulo-endothelial origin 902
Rous, influence of ferment action on infectivity of 182
round cell, of pericardium; case....*626
unusual metastases of, with existence of 2 tumors 1092
with sarcomatous stroma.... 183
Sarcosporidia, infection of myocardium in man 698
Scarlet Fever: See also Streptococcus
antitoxin in rabbits, titration of.... 177
effect of streptococci; tissue reaction effect of bacteria 895
streptococcus, effect of drying on specificity of 520
streptococcus, hemolytic, carriers of; their relation to spread of.... 519
streptococcus, in throats of diphtheria patients, incidence of.... 522
Schick Test: See under Diphtheria
Scleroderma, metabolism in.... 500
Sclerosis, coronary, in primary (essential) hypertension; 420 cases....*939
Scopometry: See Apparatus
Scurvy, influence of, on disposition to infections, experimental investigations... 528
Sebaceous Glands, tumors, polymorphism of so-called symmetrical multiple sebaceous adenomas of face.... 882
Sedimentation Reaction, Fåhräus' in phthisics in third and fourth decade, twenty-four hour value of.... 345
should it be performed before breakfast?. 345
significance of, in tuberculosis.... 170
Sella Turcica, changes in, in cerebral tumors 509
Seminal Vesicle, cysts of....1091
Septicemia, hemorrhagic, in guinea-pigs, epidemic of 718
hemorrhagic, of fish.... 749
staphylococcus 895
toxing-producing hemolytic streptococcus from 168
Serodiagnosis: See also Kahn Test
of cancer by precipitation.... 542
Serum, antithyroglobulin, action of.... 348
eel, experiments with, in isolated preparations of normal and previously treated animals 729
effect of, on germicidal action of soaps.. 164
glycerine preservation of serologic test materials, and influence of heat on glycerinated Wassermann positive serums 1128
immune, homologous, interconvertibility of R and S bacterial types of B. paratyphosus B by 743
immune, of same species, with latent period in passive anaphylaxis.... 901
immune, rabbit, relationship of precipitin and anaphylactic antibodies to protein fraction of.... 728
immune, serologic changes in paratyphoid B bacillus as influenced by growth with 336
Mollgaard's, and sodium aurothiosulphate, effect on guinea-pigs.... 170
reaction produced by feeding antigens..1113
serologic examination of patients, prospective results of.... 549
Sex, determination, by Manoilow's reaction. 341
Manoilow's Reaction for sexual hormone, alleged significance of.... 185
Shelling, D. H.: Rapid method for decalcification *835

PAGE

Sherman, I.: Hypertrophy of muscle in suprarenal vein in hypertension..... *1
Silbert, S.: Ventricular System; its relation to cerebellum: ventriculography and other ventricular evidence in recognition of cerebellar disease.....*596
Silicosis, of lung, effects of coal dust on..1087
Silver, pathology of generalized argyria; fate in human body..... 697
Singer, H. A.: Aneurysm of renal artery..*223
Skeleton, some general diseases of..... 702
Skin, capillaries, permeability of, alterations in, during course of tuberculosis..... 140
human, mineral content of..... 888
lesions, relation of acanthosis nigricans to 158
of dogs, changes in wounds of, made before and after drowning..... 907
osteosclerotic anemia secondary to epidermoid carcinoma 504
reaction, anaphylactic notes of..... 499
reactions, in normal and hypersensitive guinea-pig 899
reaction, tuberculin, value of complement-fixation test in diagnosis of tuberculosis, with special reference to its relation to 334
regenerative activity of, influence of local application of insulin on..... 501
relation of acanthosis nigricans to other lesions of 158
transplants, in relation to blood groups.. 901
Skull, injury, from electric current..... 342
Sleep, experimental exhaustion due to lack of; effect on nerve cells of spinal cord. 306
Smallpox, comparison of reactions to dermovaccine and neurovaccine for..... 531
cutaneous reaction in normal rabbit to material from lesions.....1106
prevention; tetanus following vaccination against; with special reference to use of vaccination shields and dressings.. 894
vaccination, hypersensitiveness of guinea-pigs treated with egg-white during..... 330
virus, laboratory diagnosis of..... 529
virus, laboratory diagnosis of, utilizing rabbit 1106
Smothering, suicide by..... 734

Society Transactions:

Chicago Pathological Society .....
.....346, 349, 560, 913, 1125, 1132
Minnesota Pathological Society..... 918
New York Pathological Society.....
.....187, 353, 553, 754, 925, 1136
Philadelphia Pathological Society.....
.....556, 750, 926, 1146
Society of American Bacteriologists; Twenty-Ninth Annual Meeting..... 743
Sodium aurothiosulphate, influence of, on experimental tuberculosis in rabbits 171
aurothiosulphate, Mollgaard's serum and, effect on guinea-pigs..... 170
fluoride, influence of, and of thymol, on determination of urea by urease method 1096
thiosulphate, decolorization with, resistance of tuberculosis leprosy group of organisms to; Gram stain.....*1044
Spermatocyte reaction for diagnosis of tuberculous fluids 1145
Spinal Cord, effect of experimental exhaustion due to lack of sleep on nerve cells of 306
Spine, actinomycosis of vertebrae (actinomycotic Pott's Disease) 142
angioma, lipoma and osteoma of vertebrae 884
anomaly of cervical vertebrae..... 710
Spirochaeta, cecal and bacillus, sameness between; Heliconema vincenti..... 327
icterohemorrhagic: See also Jaundice, spirochetal
icterohemorrhagic spirochaetosis of chimpanzee transmissible to man..... 525
impregnation method for Fontana-Tribondeau, modification of..... 552
in spinal fluid of syphilitic patients..... 737
new pathogenic, preliminary note on..... 720
of yellow fever, comparison of, wth leptospira of Weil's disease.....1103

Spirochaeta—Continued PAGE

pallida, reactions, specific, after injection into man 1115
Spleen, amount of blood and, relationship between 691
histologic alterations in, in chronic pulmonary tuberculosis 156
human, variations of with age..... 162
in West African Yellow fever..... 696
iron in, and in liver of fetuses and newborn babes.....1092
metastatic neoplasms in.....1089
racial variation in size of; comparison..*1040
regeneration of 1093
rôle of, in blood formation..... 875
rupture, spontaneous 701
suprarenal gland and, relation of, to cholesterol metabolism 873
tumor, of rat, due to splenic material.... 184
wandering, causing intestinal obstruction 702
Splenectomy, changes in oxygen capacity of blood pigment of rabbits following.... 888
for hemolytic icterus, recurrence of hemolytic attacks following.....1081
Splenohepatomegaly, lipoid cell, chemical analysis of spleen in..... 713
Splenomegaly, mycotic, pathologic anatomy of 150
primary granulomatous form of..... 313
Sporotrichosis, pulmonary 1098
Sputum, tuberculous, experiments with non-acid-fast micro-organism from..... 716
Stains and Staining, activity of thyroid gland in relation to staining reactions of colloid 874
Bielschowsky's nerve-stain, modification of, as applied to tumors.....1123
determination of group in human blood stain 912
effect of preliminary treatment on staining properties of tissue..... 187
Gram stain; quick method for staining gram-positive organisms in the tissues.*828
Gram stain; resistance of tuberculosis leprosy group of organisms to decolorization with sodium thiosulphate....*1044
Jessen's method for staining of tubercle bacillus and elastic fibers..... 737
origin of alveolar phagocyte studies in paraffin sections of tissue stained supravitally with neutral red..... 695
oxidase method 552
vital, identification of myeloblasts with... 711
vital, of aorta 512
Staphylococcus aureus, rate of bacterial adaptation 744
bactericidal action of blood and serum against 336
bacteriophage 167
influence of starvation and staphylococcic infection on tuberculous rabbits..... 328
sepsis 895
Starvation, staphylococcic infection and, influence of on tuberculous rabbits..... 328
Status Lymphaticus: See Lymphatism
Status Thymicolymphaticus: See Lymphatism
Stomach, changes in nerves in wall of, in chronic gastric ulcer..... 323
contents, changes in chemistry of, following gastric operations 873
duodenal flora in achlorhydria..... 748
lymphogranuloma of, hyaline bodies in.. 318
malignant papilloma of..... 751
myomas of, clinical and statistical observations on 313
peptic ulcer, changes in duodenal mucosa in 322
peptic ulcer, observation on; method of producing chronic gastric ulcer; X-ray study of experimental chronic ulcer; healing of experimental peptic ulcer after gastro-enterostomy 698
syphilitic ulcers of 878
ulcers, duodenal, jejunal and, bacteriology of peritonitis following perforation of.. 525
Strauss, I.: Subacute diffuse ependymitis; report of case simulating tumor of brain*623
Streptococcus: See also Scarlet Fever
antistreptococcus immunization and.....1105
as cause of spontaneous abortion..... 718

Streptococcus—Continued PAGE
bacteriophage 336
cardio-arthritidis, lesions produced by, compared with lesions of rheumatic fever 556, 559
effect of drying on specificity of scarlet fever 520
endocarditis, antiheterolysing serum in patient with 1114
erysipelatis, antitoxin, standardization of, on man 1112
hemolysin 533
hemolytic and anhemolytic, and B. typhosus, skin reactions to filtrates from....1112
hemolytic, antigenic complex of.....1108, 1110, 1111
hemolytic carriers; their relation to spread of scarlet fever..... 519
hemolytic, exotoxins of..... 724
hemolytic; reactions between toxins and antiserums produced with..... 742
hemolytic, toxin-producing from septicemia 168
infection in dogs, chronic, localized (experimental focal infection)..... 560
isolated from various diseases of man; immunologic specificity of..... 743
microbic dissociation in 743
mutation 528
scarlatinae, nature of toxic moiety of.... 325
scarlet fever, in throats of diphtheria patients, incidence of..... 522
toxin, in animals of different species.... 725
toxin, in strangles..... 726
transmissible toxico-genicity of..... 174
viridans endocarditis, subacute, hematology of 700
Strumia, M. M.: Modification of peroxidase reaction with sodium nitroprusside and benzidine *447
Submaxillary Glands, of guinea-pig, filtrable virus in..... 892
Sulphur, colloidal, influence of, on evolution of experimental tumors in white rats.. 338
Suprarenals, cancer, with pubertas praecox in boy aged 3 years..... 687
cortex, enlargement of, in experimental uremia in white rats..... 145
extract, epinephrine hydrochloride and hemopoiesis 513
extract, pilocarpine and epinephrine, effect of, in production of specific lesions in stomach of rabbits.....*411
extract, relationship of glycogen formation in muscles to pancreas and.....1079
hemorrhage 878
reaction, to local injury..... 709
spleen and, relation of to cholesterol metabolism 873
water and lipoid content of..... 159
Surgical pathology and surgeon, 346, 347, 348
Symbiosis, bacterial, gas production by, with special reference to influence of nitrogenous substances 333
Synovial Fluid, chemical composition of, in joint effusion 1095
Synovial Membrane, tumors, synoviomas.. 505
Synthalin, effects of on metabolism..... 688
Syphilis, autolysin in blood of patients with 181
bloodclot Wassermann reaction of Dold 186
experimental, in new-born rabbits..... 330
globulins in relation to Wassermann and Sachs-Georgi reactions 541
hemorrhagic, of lower extremities; clinical variety of; pigmented and purpuric dermatitis of legs..... 880
in domestic camel, negative attempts to reproduce it..... 721
infection from cadaver 305
influence of, on incidence of pneumococcus types in lobar pneumonia.....1146
involvement of aortic valve in syphilitic aortitis 696
Kolmer-Wassermann reaction, reliability of, in pregnancy 1122
microprecipitation test for.....*445
pulmonary tuberculosis and, coexistence of in 659 cases, with 125 autopsies..... 715

Syphilis—Continued PAGE
serodiagnosis: See also Kahn Test; Kolmer-Wassermann Reaction; Meinicke's Reaction; Sachs-Georgi Reaction; Wassermann Reaction, etc.
serodiagnosis of, by Meinicke's macroreaction and microreaction.....1124
ulcerations of stomach..... 878
vascular, unusual forms of..... 885

Taenia crassicollis, larvae, transplantation and experimental production of subcutaneous cysticercus sarcomata..... 530
Takata-Ara's Test: See under Cerebrospinal Fluid
Tar from rice polishing; epithelium-producing constituents 185
Telangiectases and allied conditions, irresponsive condition of vessels, pathology of 498
Teratoma of testis, spontaneous healing of.. 543
Testicle, changes in, gynecomastia associated with 161
infarction 701
malignant tumors of..... 901
teratoma of, spontaneous healing of..... 543
Tetanospasmin and tetanolysin..... 528
Tetanus following sand flea bites..... 722
following vaccination against smallpox, and its prevention; use of vaccination shields and dressings 894
spores, conditions under which germination occurs in vivo..... 524
spores, inoculated into guinea-pigs, local fate of 524
toxin, tetanospasmin and tetanolysin.... 537
Tetany, calcium ion concentration during pregnancy and its relation to..... 889
infantile, effect of parathyroid extract on mineral metabolism in..... 1079
Thoracic Duct, thrombolymphangitis of.... 156
Thorax, neoplasm of..... 312
Thrombolymphangitis of thoracic ducts.... 156
Thrombosis, cavernous, transformation of portal vein, case..... 554
embolism and, of lungs, increasing number of deaths from..... 883
experimental, extracorporeal.....145, 1085
peculiar reaction of vascular endothelium associated with..... 887
Thymus: See also Lymphatism
Thymus, carcinoma of..... 733
crossed dystopia of..... 318
malignant tumor of; case..... 928
status thymicolymphaticus, recent work on 311
Thyroid, activity of, in relation to staining reactions of colloid..... 874
apparatus 497
extracts, comparison in normal thyroidectomized and hypophysectomized rats of effect on metabolism and growth resultfrom daily injections of small amounts of 684
fat contents of pathologic thyroids in man; histologic studies *13
hyperthyroidism, experimental 306
hypothyroidism, extreme, rachitic-like disturbance in 497
influence of, on production and control of experimental rickets 872
malignant disease of.....1082
pancreas and, alleged interrelationship of 685
primary hypertension and associated hyperthyroidism; 3 cases..... 918
therapy, effect of, on children.....1079
tumors, in mice, relation of heredity to; incidence and inheritability of spontaneous tumors in mice..... 731
Thyroidectomy, basal metabolism in simple and cystic adenomatous goiter in relation to 1081
influence of, on anaphylactic shock..... 539
pulmonary atelectasis following; 4 cases with observations at necropsy.....*763
Thyroxin, constitution and synthesis of.... 889
synthetic, physiologic test of..... 889
Tissue, adipose, in pleura, formation of.... 507
effect of extracts on red blood cell regeneration in rabbit..... 874
effect of preliminary treatment on staining properties of 187

Tissue—Continued PAGE
formation of giant cell epulis..... 158
normal, potassium and calcium content of, and distribution in..... 553
perivascular, of central nervous system with supravital technic..... 146
quick celloidin method for preparing.....*282
Tissue, storage of water by..... 515
tumor, inoculated, pyogenic action of... 339
tumor, insulin in..... 338
Trachea, primary complex in adult, with focal tuberculin reaction in tracheobronchial lymph nodes; case..... 715
tracheopathia, chondro-osteoplastica..... 156
tracheopathia osteoplastica 513
Transplantation: See also Tumors
free, of upper extremity, through amniogenic malformation 320
individuality differentials and, in inbred families of guinea-pigs..... 504
Trauma, relation of, to neoplasm considered from a medicolegal point of view..... 908
to head and feet, in hanging; late cerebral hemorrhage following blow on head; voluntary stripping out of colon; unusual medicolegal experiences..... 546
Trichinosis, myocarditis in..... 885
Trichocephalus dispar, pathogenic rôle of.. 324
Trichuris Trichiura: See Trichocephalus Dispar
Tropical Medicine: See under names of tropical diseases, as Leishmaniasis
Tubercle Bacillus, bovine, in immunization 899
bovine, relation of monocytes and clasmatocytes to early infection in rabbits with 146
cultivation of, and use in diagnosis of tuberculosis 525, 526
cultivation of, in diagnosis of tuberculosis 552
elimination of specific substance of, in tuberculous animals 173
filtrability of 1100
filtrable forms of, and of protective substances in filtrates, investigation of; experiments with filtrates of tuberculous sputum 716
formation of radial rows of clubs about dead tubercle bacillus as reaction of host 527
Gram stain on; resistance of tuberculosis leprosy group of organisms to decolorization with sodium thiosulphate.....*1044
granules of..... 1099
Hohn method for cultivation of..... 552
human, chemical analysis of; reactions in rabbits to protein and phosphatid fractions from 146
inflammatory process, nature of..... 721
isolation of, according to Hohn, in its practical application for bacteriologic and clinical diagnosis.....1124
isolation of, from contaminated tuberculosis materials 716
isolation of, from septic material.....1099
microbic dissociation of..... 744
new mediums for culture of.....1133
new stain for 185
nonprotein antigen of..... 173
practical technic in preparation of smears for examination of..... 551
relation between loss of acid-fastness of, and hydrogen-ion concentration.....1099
relation of glycerol in culture mediums to growth and chemical composition of. 717
simultaneous specific staining of, elastic fibers and, after Jessen's method..... 737
stained, in light-dark field, microscopic demonstration of..... 345
Tuberculin, electrodialysis of.....1095
experimental immunization of normal guinea-pigs with serum albumin plus.. 729
papules, demonstration of procutines in.. 178
provocatory administration, behavior of blood sedimentation after..... 170
reaction in tracheobronchial lymph nodes, case of primary complex in adult with. 715
Tuberculoma, healed, of cerebellum.....1087
large, calcified, of cerebrum, with independent terminal cerebral hemorrhage.1087
Tuberculosis, alterations in permeability of skin capillaries during course of..... 140
bacterial etiology of; experiments with

Tuberculosis—Continued PAGE
non-acid-fast micro-organisms from tuberculous sputum..... 716
blastomycosis and; similarity of reticulum in lung in..... 505
blood groups in 174, 181, 334
blood picture, white, of tuberculous guinea-pig 328
blood refraction and colloid lability in.. 173
calcium and vitamine D deficiencies as factors in lowering resistance to, in white rats 1099
cerebral, in adults; cases..... 875
chemical studies in..... 519
diagnosis of, cultivation of tubercle bacillus and its use in.....525, 526, 552
epidemiology of 723
experimental, in rabbits, influence of sodium aurothiosulphate on..... 171
experimental, in rats on varied diets..... 165
experimental, of rabbits, gold treatment in 172
experimental, of rabbits, sanocrysin treatment in 896
fibrocaseous, of lymph gland..... 155
foci, formation of, after intratracheal infection of rabbits..... 171
genital, in females; primary, fallopian tube 155
granulation tissue in, lipase in 1097
grave, in children, and relation between tuberculosis in children and later chronic pulmonary tuberculosis..... 172
immunity, freezing B C G for transportation over great distances..... 740
immunity of guinea-pigs against enteral infection by human tuberculosis bacillus after intragastric administration of B C G Calmette-Guérin.....1114
immunity, preventive inoculation, with Calmette's B C G.....540, 727
immunity, serum studies on isolated vascular preparations of normal anaphylactic and tuberculous animals..... 727
immunity, transfer of local hypersensitiveness of tuberculous guinea-pigs with blood serum 330
immunity, vaccination with B C G in guinea-pigs 725, 1114
immunization, attempts at, with B C G Calmette-Guérin 1114
immunization of new-born with B C G.. 533
in bone marrow of rabbits, correlated with transitory anemia and leukopenia after intravenous inoculation, local progression with spontaneous regression of... 325
infarct-like areas in kidneys of tuberculous persons 510
influence of starvation and staphylococcic infection on tuberculous rabbits.... 328
intestinal, relation to course of pulmonary tuberculosis 896
late caseation of lymph glands and Ranke's stages in 172
latent, reactivation of and its cause..... 155
lesions of, giant cells of; binucleate and giant cells in tissue cultures; similarity of latter to 312
lipolytic ferment of blood, lymphocytes and Pirquet's reaction in 180
of children, primary complex in..... 163
of urethra 162
pulmonary, basal metabolism in....872, 1081
pulmonary, blood sugar in..... 518
pulmonary, bronchomycoses simulating..1098
pulmonary, chronic; histologic alterations in spleen 156
pulmonary, course of, relation of intestinal tuberculosis to..... 896
pulmonary, hemorrhage in, pathogenesis of 156
pulmonary, parafocal cavities in..... 156
pulmonary, parenchymal, in children.... 165
pulmonary, syphilis and, coexistence of, in 659 cases, with 125 autopsies..... 715
pulmonary, thrombocytes in..... 172
pulmonary, under sanocrysin, treatment chemical urinary studies on patients with 887
pulmonary, viscosity of blood in..... 170
researches 1918-1926 896
sanocrysin in, microhistochemical gold reactions after use of..... 163

Tuberculosis—Continued PAGE
secondary myelosis in 708
sedimentation reaction in,..... 171
serodiagnosis, complement fixation according to Besredka, Matify's reaction and sedimentation rate 335
serodiagnosis, complement fixation, antigen in 724
serodiagnosis, complement fixation test, value of, in diagnosis of tuberculosis; its relation to tuberculin skin reaction. 334
serodiagnosis, complement fixation, with simplified antigen 181
serodiagnosis, Neuberg-Klopstock and Lehmann-Facius-Loeschke reactions.... 335
serodiagnosis, serologic measure of..... 173
serodiagnosis, spermatocyte reaction for diagnosis of tuberculous fluids.....1145
serodiagnosis, Vernes' flocculation test; results in 250 cases..... 927
serodiagnosis, Vernes' test..... 174
serodiagnosis, Wassermann reaction..... 334
spontaneous, of rabbits.....1146
transmission, significance of cough droplets and dry dust in..... 165
transmission, through domestic animals.. 165
Tularemia among meadow mice in California 1103
microscopic changes of, in tick dermacentor andersoni and bedbug cimex lectularius 719
tularemic peritonitis 520
Tumors: See also Cancer; Sarcoma; and under names of tumors
experimental, in white rats, influence of colloidal sulphur on evolution of..... 338
formation, infection and parasitism..903, 904
formation, relation of trauma to neoplasm, considered from a medicolegal point of view 908
formation, relative p_H of mammalian tissues and possible rôle in..... 542
giant cell, in metacarpal bone..... 699
growth, innervation and.....1123
in rabbit 732
in rat, due to splenic material..... 184
in scar of cock on which operation was performed 1119
indol, Carrel, immunity of fowls against. 541
inoculable, relation of plasma sodium content of mice to their susceptibility to..1118
malignant, caused by tar..... 733
malignant, heterotransplantation of..... 339
malignant, of testicle..... 901
malignant, local eosinophilia in..... 338
malignant, simulating bone marrow.....1117
malignant thymoma; case..... 928
massage and metastases in mice..... 732
metabolism, carbohydrate 184
metabolism, in body..... 337
metastatic, in brain, location of..... 561
mixed, of molar glands..... 183
mixed, of uterus, with metastases to tibia 150
of endocardium 317
of carotid body..... 707
of intestine 702
of lungs, in horse and in donkey.....1119
of pineal gland.....1083
of thyroid, spontaneous, in mice, relation of heredity to..... 731
regeneration 905
spontaneous, incidence and inheritability of, in mice.....731, 1118
staining, Bielschowsky's nerve stain, modification of, as applied to.....1123
tar, of chickens..... 184
transplantable, breakdown of hereditary immunity to, by introduction of irritant agent 542
vascular patterns of..... 182
Twins, single ovum, identification characters of 160
Typhoid, bacillus, duodenal aspirations for, in typhoid fever..... 722
bacillus, in immune reactions, rôle of ectoplasm and endoplasm of..180, 336, 729
bacillus, precipitable substances derived from, and from B. paratyphosus B....1109
bacillus skin reactions to filtrates from...1112
diagnosis of, by intradermal reaction.... 535
Typhoid—Continued PAGE
duodenal aspirations for typhoid bacillus in 722
incubation period 1106
vaccine 900
Typhus 720
serology of 174

Ultraviolet Rays, absorption spectra of certain physiologic fluids..... 551
effects of 499
effect of, on blood of new-born infants... 496
vaccine virus and.....1101
Underhill, F. P.: Effect of pilocarpine and epinephrine in production of specific lesions in stomach of rabbits.....*411
Undulant Fever: See Malta Fever
Uranium, effect of arteriosclerosis and nephritis caused by, on blood pressure of rabbit; influence of other heavy metals *577
Urea, determination by urease method, influence of sodium fluoride and thymol on 1096
effects of, on living cells..... 746
Urease, determination of urea by gasometric measurement of carbon dioxide formed by action of..... 323
method of urea determination, influence of sodium fluoride and thymol on.....1096
Uremia, experimental, enlargement of suprarenal cortex in white rats..... 145
free and conjugated phenols in blood and spinal fluid of patients with, and xanthoprotein reaction 712
hydrogen sulphide in blood in..... 518
Urethra, dilatation, septic embolism following 907
tuberculosis of 162
Uric Acid, test for..... 911
Urinary Tract, calculi, vitamin A deficiency and 873
gangrene of urinary bladder..... 752
Urine, acid-base composition of, from epileptic child 711
acidity of, and method for electrometric titration of 344
chlorides, effect of overbreathing and of breathing relatively high concentrations of carbon dioxide, on urinary excretion of water and chlorides..... 874
hormone test of, diagnosis of pregnancy by 911
phosphates, inorganic, influence of purine diuretics on 1096
pigment, normal, relationship of basal metabolism to output of..... 688
Urobilin, physiology and pathology..... 498
Uterus: See also Endometrium
cervix, epidermidalization of, and its relation to malignancy.....1117
cirsoid aneurysm of..... 694
mixed tumor of with metastases to tibia.. 150
myosarcoma of, histologic study of femoral metastasis from 902
postpartum, involution of..... 147

Vaccination, oral, subcutaneous and intravenous with native fetal organisms.... 746
Vaccine, B C G, against tuberculosis, in guinea-pigs 1114
B C G, Calmette-Guérin, attempts to immunize with 1114
B C G, Calmette-Guérin, intragastric administration of, immunity of guinea-pigs against enteral infection by human tuberculosis bacillus after.....1114
B C G, Calmette's preventive inoculation against tuberculosis with..... 540
B C G, freezing, for transportation over great distances 740
B C G, immunization of new-born with... 533
B C G, in guinea-pigs..... 725
typhoid 900
virus, observations on..... 893
virus, susceptibility of fowls and reptiles to 518
virus, ultraviolet light and.....1101
Vaccination, against Pasteurella avicida, comparison of effectiveness of, oral, subcutaneous and intravenous methods. 746

PAGE

Vein, hepatic, obliteration of principal..... 514
portal, cavernous transformation of; case 554
suprarenal, in hypertension; hypertrophy of muscle in..... *1
Venom, cobra, action of light on..... 900
cobra, effect of, on action of lipoid antibodies 728
Vernes' Test, flocculation, for tuberculosis; results of 250 cases..... 927
for tuberculosis 174
Verruca, mycotic warts..... 166
Verruga Peruana: See Oroya Fever
Viruses, chicken tumor, inactivation of, by means of aluminum compounds..... 182
filtrable, bacteriophage as..... 756
filtrable; critical review..... 717
filtrable, in submaxillary glands of guinea-pig 892
invisible, separation of from concomitant bacillus 186
Rous, sarcoma, specificity of, as tested by experimental embryoma in chickens.... 182
smallpox, laboratory diagnosis of..... 529
Viscera, injuries, due to jumping or falling from high places into water..... 342
Vital Statistics, report of Chief Medical Examiner of New York City..... 340
Vitamins, A, deficiency in guinea-pig.....*239
A, deficiency, metaplasia and..... 689
A, deficiency, urolithiasis and..... 873
D, deficiency and calcium deficiency, as factors in lowering resistance to tuberculosis in white rats.....1099

Waddell, K. C.: Effects of high-voltage cathode rays on skin of rat.....*195
Wassermann Reaction, agglutinin reaction and, with serum from patients with febrile diseases 532
experiences with tuberculosis reaction according to 334

Wassermann Reaction—Continued PAGE
glycerine preservation of serologic test materials, and influence of heat on glycerinated Wassermann positive serums.1128
in cerebrospinal fluids containing blood.. 551
of Dold, on bloodclots..... 186
with large amounts of serum..... 912
Water, metabolism and quenching of thirst. 501
storage of, by various tissues of body.... 515
tap, leptospiras from..... 167
Watson, E. M.: Aid in testing gastric contents for lactic acid..... *66
Weil's Disease: See Jaundice
Whitlow: See Paronychia
Whooping Cough, pathologic anatomy of lung in 1092
potency of stored pertussis vaccines..... 332
Wolbach, S. B.: Malignant rhabdomyoma of skeletal muscle.....*775
Vitamin A deficiency in guinea-pig.....*239
Woods, A. H.: Fracture into frontal sinuses with discharge of cerebrospinal fluid for over year; report of case with death from pneumococcus meningitis..*6[illegible]
Wounds, bullet, rupture of aorta following. *548
dirt in, importance of ascertaining character of 736

Xanthoma, isolated giant cell xanthomatic tumors of fingers and hand..... 877
xanthomatosis, cholesterolemia and familial cholelithiasis 507
Xanthoprotein: See Blood

Yellow Fever, anatomic diagnosis of.....1103
comparison of spirochete of, with leptospira of Weil's disease.....1103
spleen in, in West Africa..... 696
Weil's Disease and..... 890

Zinc, normal nutrition and..... 688
stearate insufflation 544

JUN 2 0 1928

VOL. 5 NUMBER 6

ARCHIVES of PATHOLOGY

EDITORIAL BOARD

[illegible], CHICAGO
JAMES EWING, NEW YORK
WILLIAM OPHÜLS, SAN FRANCISCO
[illegible] WOLBACH, BOSTON
W. G. MacCALLUM, BALTIMORE
[illegible] STENGEL, PHILADELPHIA
OSCAR T. SCHULTZ, CHICAGO

JUNE, 1928

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter Jan. 21, [illegible] at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for [illegible] at special rate of postage provided for in Sec. 412, Act of Feb. [illegible] authorized Jan. 21, [illegible]

THE ARCHIVES OF PATHOLOGY is published by the American Medical Association as a medium to advance the science of pathology in the United States and for the promotion of research and observation in this field.

Manuscripts for publication, books for review, and correspondence relating to contributions should be sent to Dr. [illegible] Hektoen, 637 South Wood Street, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed: Archives of Pathology, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the Archives of Pathology. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Line etchings and halftone illustrations will be supplied by the publisher when the circulation relations warrant.

Abbreviations and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, published by the American Medical Association. This requires, in order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. A complete list of abbreviations for standard periodicals, together with a full discussion of the style of the A. M. A. publications, appears in The Standard Practice of Medical Writing, a comprehensive book on the preparation of medical manuscripts, published by the American Medical Association. Price, $1.50.

Matter appearing in the ARCHIVES OF PATHOLOGY is covered by copyright, but, as a rule, no objection will be made to its reproduction in reputable medical journals if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the ARCHIVES OF PATHOLOGY, or in any of the other publications issued by the Association, will not be permitted.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The ARCHIVES OF PATHOLOGY is published monthly. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75, including postage. Single copies, 75 cents, postpaid.

Checks, etc. should be made payable to the AMERICAN MEDICAL ASSOCIATION.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $7.50. Single copies, 20 cents.

ARCHIVES OF INTERNAL MEDICINE—Monthly. Devoted to the publication of advanced, original clinical and laboratory investigation in internal medicine. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Pediatrics as a medical science and as a special practice. Includes carefully prepared collective abstracts based on current pediatric literature, abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 65 cents.

ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Published original contributions and abstracts of the literature on these subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 65 cents.

ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews of progress and special articles. Well illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 65 cents.

ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, the transactions of societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

QUARTERLY CUMULATIVE INDEX MEDICUS—Quarterly. A complete subject and author index to the world's current medical literature. Issued four times a year. Second and fourth volumes bound for permanent reference. Subscription price, calendar year: Domestic, $5.00; Canadian, $5.50; foreign, $5.75.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn St. CHICAGO